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كلية الدراسات العليا

التاريـــخ: / /

نموذج رقم (18)
اقرار والتزام بالمعايير الأخلاقية والأمانة العلمية
وقوانين الجامعة الأردنية وأنظمتها وتعليماتها
لطلبة الماجستير

أنا الطالب: إبراهيم صالح احمد ذياب — الرقم الجامعي: (8060375)

تخصص: الكيمياء — الكليـــــــة: العلوم

عنوان الرسالة:

"Water-Soluble Platinum Complexes as Anti-Cancer Drugs"

اعلن بأنني قد التزمت بقوانين الجامعة الأردنية وأنظمتها وتعليماتها وقراراتها السارية المفعول المتعلقة باعداد رسائل الماجستير عندما قمت شخصيا" باعداد رسالتي وذلك بما ينسجم مع الأمانة العلمية وكافة المعايير الأخلاقية المتعارف عليها في كتابة الرسائل العلمية. كما أنني أعلن بأن رسالتي هذه غير منقولة أو مستلة من رسائل أو كتب أو أبحاث أو أي منشورات علمية تم نشرها أو تخزينها في أي وسيلة اعلامية، وتأسيسا" على ما تقدم فانني أتحمل المسؤولية بأنواعها كافة فيما لو تبين غير ذلك بما فيه حق مجلس العمداء في الجامعة الأردنية بالغاء قرار منحي الدرجة العلمية التي حصلت عليها وسحب شهادة التخرج مني بعد صدورها دون أن يكون لي أي حق في التظلم أو الاعتراض أو الطعن بأي صورة كانت في القرار الصادر عن مجلس العمداء بهذا الصدد.

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WATER-SOLUBLE PLATINUM COMPLEXES AS ANTI-CANCER DRUGS

By

Ibrahim Saleh Diab

Supervisor

Dr. Hamdallah A. Hodali, Prof.

This Thesis was Submitted in Partial Fulfillment of the Requirements for the Master's Degree of Science in Chemistry

Faculty of Graduate Studies

The University of Jordan

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August, 2011

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COMMITTEE DECISION

This Thesis/Dissertation (Water-Soluble Platinum Complexes as Anti-Cancer Drugs) was Successfully Defended and Approved on 21/7/2011.

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DEDICATION

To My Lovely Family

Mother,

Father,

Sister

and

Brothers.

To My FIANCEE

AND

Close Friends…

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AKNOWLEDGEMENTS

First of all, I would like to thank **ALLAH**, who guided me and gave me this chance to reach this achievement and to whom I submit my life and soul. Secondly, I would like to thank Prof. Hamdallah A. Hodali and send him my deepest appreciation for his patience, tolerance, support, guidance, wisdom and scientific knowledge through the course of thesis.

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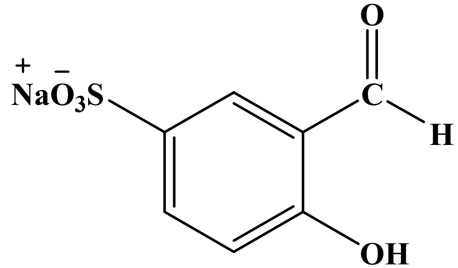
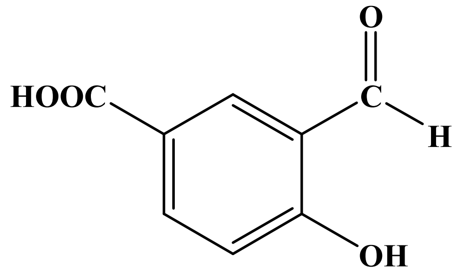
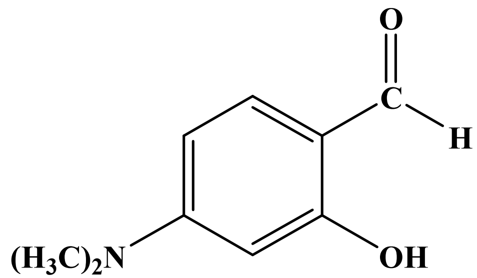
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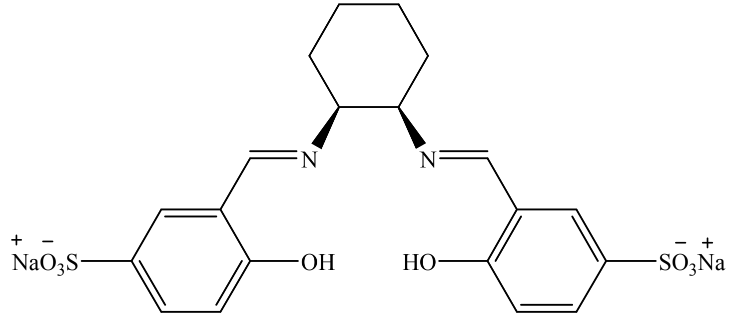
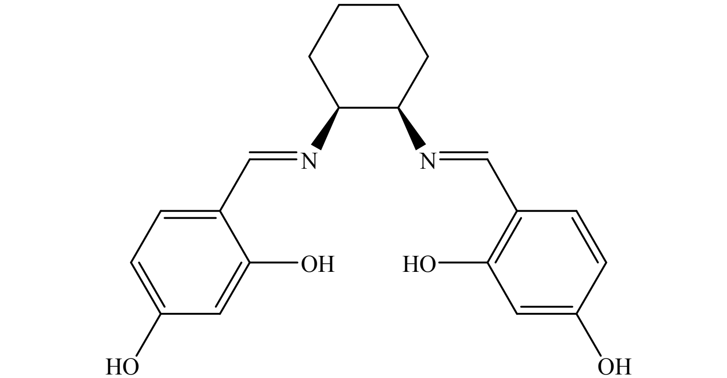
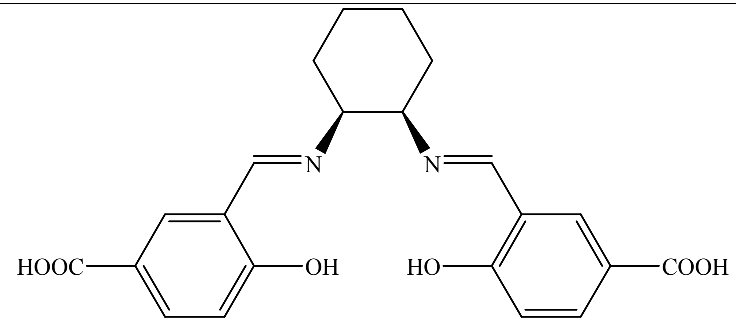
***cis*-DACH.2HCl:**	*cis*-1,2-Diaminocyclohexane dihydrochloride.
***trans*-DACH.2HCl:**	*trans*-1,2-Diaminocyclohexane dihydrochloride.
DHBA	2,4-Dihydroxybenzaldehyde.
SAR:	Structure/Activity Relationships.
DMSO:	Dimethylsulfoxide.
DMF:	N,N-Dimethylformamide.
DEPT-135	Distortionless Enhancement By Polarization Transfer.

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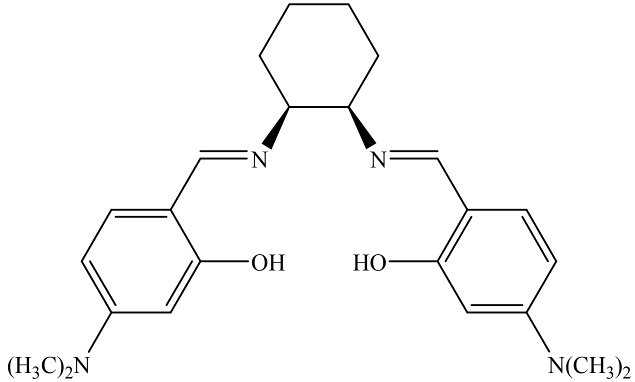
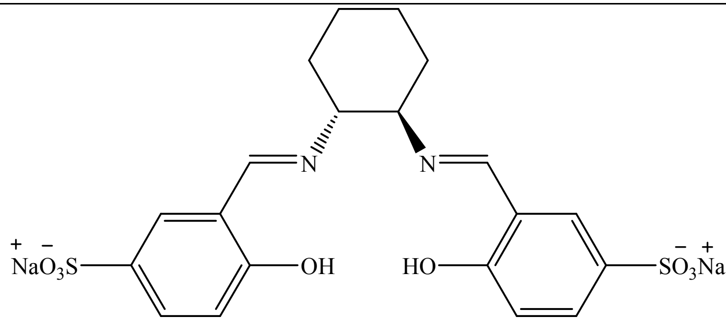
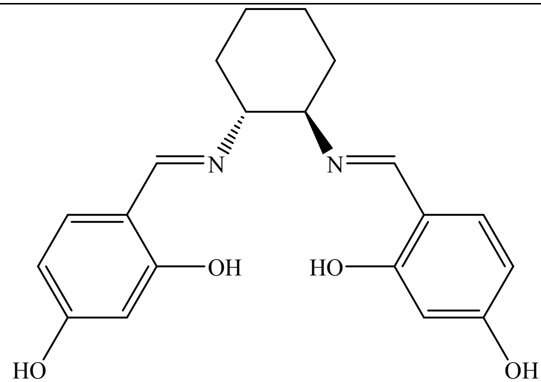
LIST OF COMPOUNDS

I. D. No.	Name	Structure
I	Sodium Salt of Salicylaldehyde-5-sulfonic Acid	
II	3-Formyl-4-hydroxybenzoic Acid	
III	4-(N,N-Dimethylamino)salicylaldehyde	

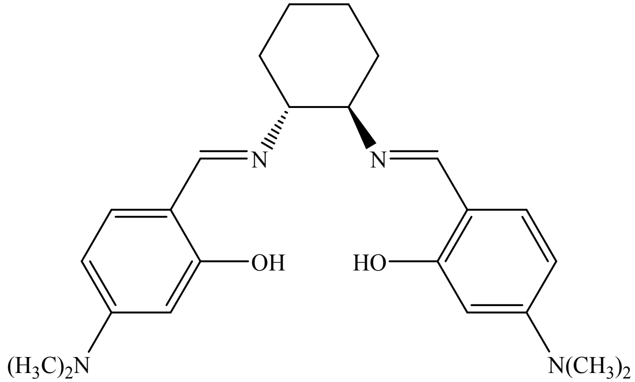
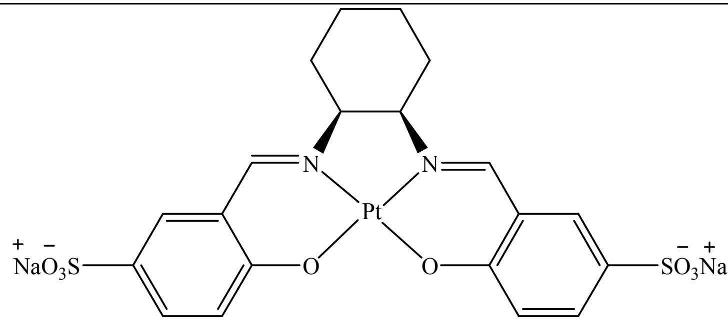
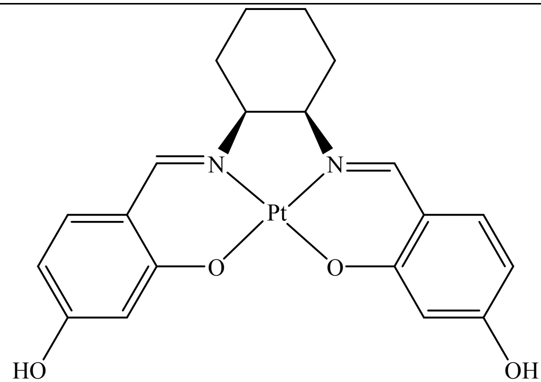
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IV	Disodium Salt of 3,3'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethylidyne) -bis-4-hydroxybenzenesulfonic Acid	
V	4,4'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]bis-1,3-benzenediol	
VI	3,3'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]bis-4-hydroxy-benzoic Acid	

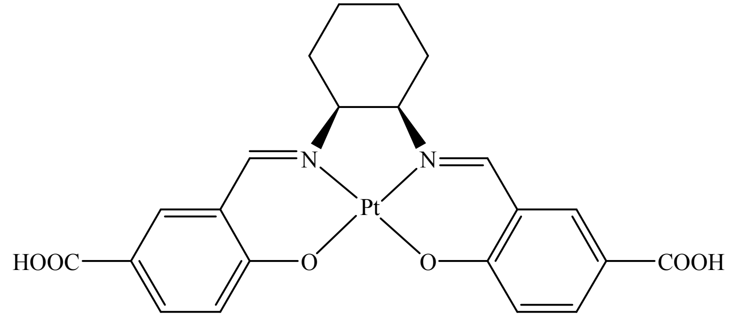
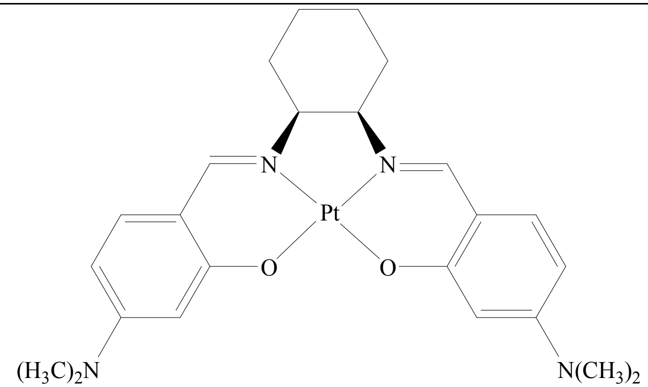
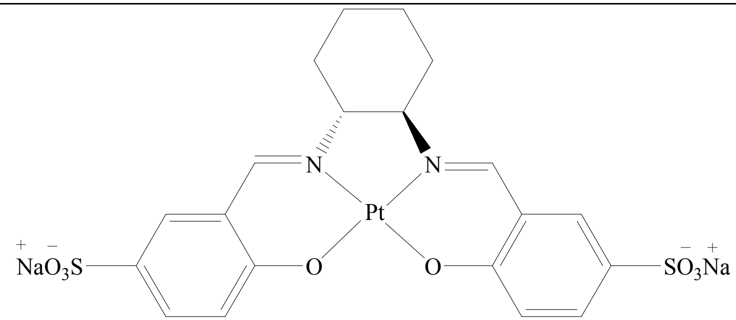
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VII	2,2'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]bis-[5-(N,N)-(dimethylamino)phenol]	
VIII	Disodium Salt of 3,3'-[*trans*-1,2-Cyclohexanediylbis-(nitrilomethylidyne)]bis-4-hydroxybenzenesulfonic Acid	
IX	4,4'-[*trans*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]-bis-1,3-benzenediol	

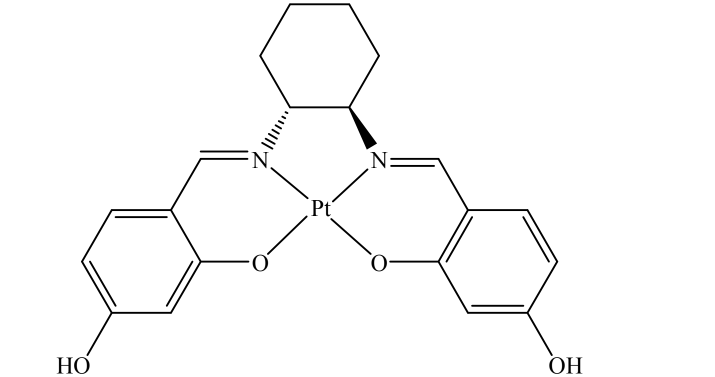
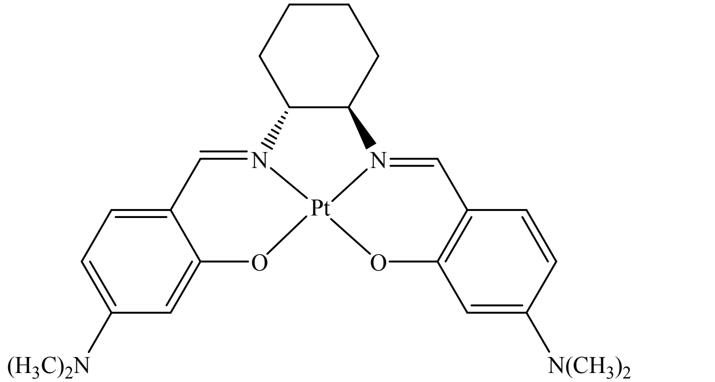
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X	2,2'-[*trans*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]-bis-[5-(N,N)-(dimethylamino)phenol]	
XI	Sodium [3,3'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]] bis[4-(hydroxy-κO)benzenesulfonato]]-platinate(II)	
XII	[4,4'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)-methylidyne]]bis-[1,3-benzenediolato-κO3]]platinum(II)	

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XIII	[3,3'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[4-(hydroxyl-κO)benzoato]]platinum(II)	
XIV	[2,2'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[5-(dimethylamino)phenolato-κO]]platinum(II)	
XV	Sodium [3,3'-[*trans*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]] bis-[4-(hydroxy-κO)benzenesulfonato]] platinate(II)	

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XVI	[4,4'-[*trans*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis[1,3-benzenediolato-κO3]]platinum(II)	
XVII	[2,2'-[*trans*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[5-(dimethylamino)phenolato-κO]]platinum(II)	

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WATER-SOLUBLE PLATINUM COMPLEXES AS ANTI-CANCER DRUGS

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ABSTRACT

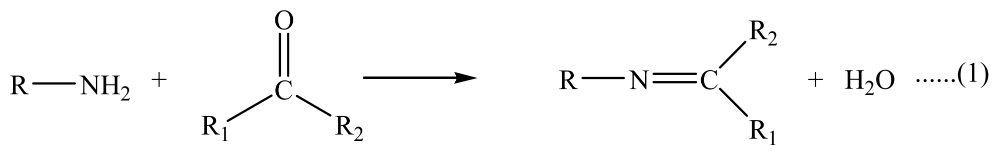
The tetradentate Schiff base ligands, disodium salt of 3,3'-[*cis*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-4-hydroxybenzenesulfonic acid **(IV)**, 4,4'-[*cis*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-1,3-benzenediol **(V)**, 3,3'-[*cis*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-4-hydroxybenzoic acid **(VI)**, 2,2'-[*cis*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-[5-(N,N)-(dimethylamino)phenol] **(VII)**, disodium salt of 3,3'-[*trans*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis4-hydroxybenzenesulfonic acid **(VIII)**, 4,4'-[*trans*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-1,3-benzenediol, **(IX)** and 2,2'-[*trans*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-[5-(N,N)-(dimethylamino)phenol] **(X)**, have been prepared by the condensation of suitable substituted salicylaldehydes with *cis*- and *trans*-1,2-diamincyclohexane in a 2:1 molar ratio. The substituents (sulfonyl, hydroxyl, carboxyl and dimethylamino) are chosen in a way to increase the hydrophilic character of the Schiff bases and consequently the solubility of their platinum complexes in water. The above ligands have been characterized by IR, ^{1}H-NMR and ^{13}C-NMR. Their reactions with potassium tetrachloroplatinate(II) [K_2PtCl_4] in the presence of anhydrous sodium acetate (CH_3COONa) gave **(XI)**, **(XII)**, **(XIII)**, **(XIV)**, **(XV)**, **(XVI)** and **(XVII)**, respectively. These complexes have been characterized by IR, ^{1}H-NMR, ^{13}C-NMR Some of these complexes have shown good solubility in water and expected to have good activity and lower toxicity as anti-cancer drugs.

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1. INTRODUCTION

1.1 Schiff Bases:

Schiff bases are compounds with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom bonded to an alkyl group and not a hydrogen atom. According to this definition Schiff bases, with the general formula R_1CR_2=NR, are subclass of azomethine compounds. They are produced by condensation reaction of a primary amine with an aldehyde or a ketone (Hansen, et al., 2009):



where: R = Alkyl, R_1= R_2 : H, Alkyl

1.2 Historical Background:

Schiff bases are considered an important class of compounds for their applications in chemical analyses (Jungreis, 1969), catalytic reactions (Guerriero, et al., 1992), medicinal and pharmaceutical fields (Shahabadi, et al., 2010). Schiff base complexes of transition metals are also of importance and have a variety of applications in biological (Mandal, et al., 1996), catalytical (Sun and Tang, 2006), analytical and clinical aspects (Gabella, et al., 2007).

Tetradentate Schiff base ligands have attracted the attention of many researchers. Among the widely known tetradentate Schiff base ligands are the salen ligands. A typical example of these ligands is: 2,2'-[1,2-ethandiyl-bis(nitrilomethylidyne)]bisphenol (Fig. 1.1) (Koley, et al., 2010).

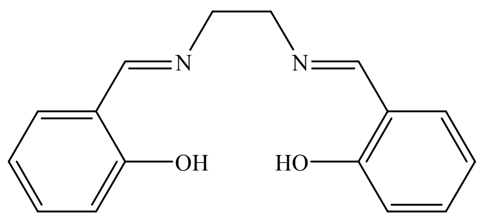
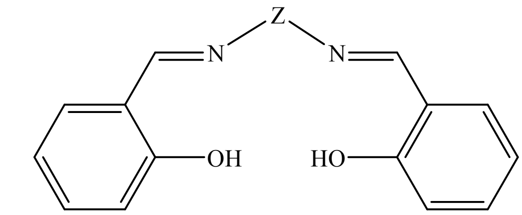


Figure 1.1: A typical example of salen ligand

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Other structurally related tetradentate Schiff bases have been prepared and characterized, (Fig. 1.2) (Gravert and Griffin, 1996).

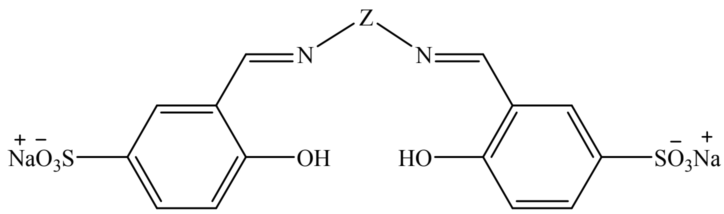


where: Z = $CH_2CH_2CH_2$, *o*-C_6H_4, *cis*-C_6H_{12}, *trans*-C_6H_{12}, $CH(C_6H_5)CH(C_6H_5)$

Figure 1.2: Tetradentate Schiff Base Ligands with Diamine Compounds

Salen metal complexes are utilized in many catalytic applications including Diels-Alder transformations (Bandini, et al., 2002), olefin epoxidation (Sun and Tang, 2006), electrochemical reductions (Shearer and Rosita, 1990), benzylic hydroxylation (Hamada, et al., 1998) and nucleic acid modification (Routier, et al., 1997).

In general, unsubstituted salens and their transition-metal complexes are insoluble in water, which limits their uses in medicinal applications (Liu, et al., 2007). Some substituents on the benzene ring of the starting aldehyde, such as the sulfonyl group (Fig. 1.3), enhance the water solubility of the ligands and consequently their metal complexes (Corria, et al., 2006).



where: Z = $CH_2CH_2CH_2$, *o*-C_6H_4, *trans*-C_6H_{12}, $CH(C_6H_5)CH(C_6H_5)$

Figure 1.3: Examples of sulfonated salens ligands

1.3 Water-Soluble Tetradentate Schiff Bases:

It has been found that introducing certain substituents on the salen ligands enhances their water solubility (Evans and Missen, 1987). The easiest way is to start with substituted salicylaldehyde. Among the substituents on the salicylaldehyde are the sulfonyl group ($-SO_3Na$) (Moreno, et al., 2010; Wu, et al., 2010), carboxyl groups

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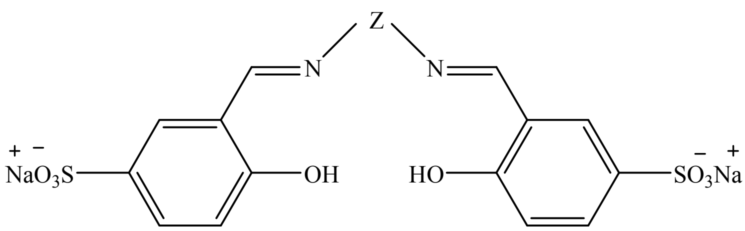
(-COOH) or (-COONa) (Cheng and Liu, 2000), hydroxyl groups (-OH) (Niasari and Bazarganipour, 2009) and ammonium groups ($-^{+}NR_3$) (Muller, et al., 1999; Bahramian et al., 2006).

For example, using salicylaldehyde-5-sulphonate in place of salicylaldehyde affords a water-soluble ligand and consequently forms water-soluble metal complex (Berry, et al., 1982).

Water-soluble metal complexes of Schiff bases have crucial applications in biological systems (Moreno, et al., 2010), pharmaceutical activities (Liu, et al., 2007), chemical analyses (Shiri-Yekta, et al., 2009), homogeneous and heterogeneous catalysis (Correia, et al., 2006), oxidation of alcohols (Bahramian, et al., 2006) and anti-tumor agents (Ansari, et al., 2009).

1.3.1 Schiff Bases Containing Sulfonyl Groups:

Many sulfonated Schiff bases derived from substituted salicylaldehydes and primary amines were prepared in the literature (Corria, et al., 2005; Salanti, et al., 2010; Wu, et al., 2010). Examples of these are shown in Fig. 1.4a and Fig. 1.4b (Moreno, et al., 2010).



where: (a) Z = CH_2CH_2, *trans*-C_6H_{12}, *o*-C_6H_4
(b) Z = $CH_2CH_2CH_2$, $CH_2CH(OH)CH_2$

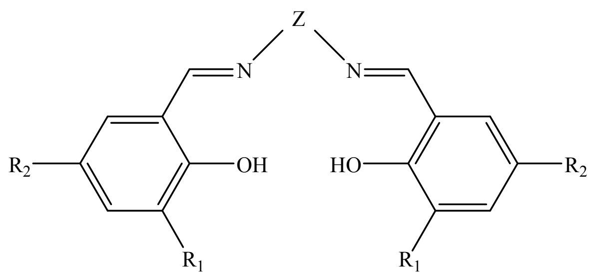
Figure 1.4: Examples of sulfonated tetradentate Schiff bases

The Schiff bases in Fig. 1.4 were prepared by condensation of the Compound **(I)** salt with suitable diamine in absolute ethanol in 2:1 molar ratio (Corria, et al., 2005; Moreno, et al., 2010).

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1.3.2 Schiff Bases Containing Carboxyl Groups:

Tetradentate Schiff bases containing carboxyl groups are prepared from the condensation of 3-formyl-4-hydroxybenzoic acid (Compound **(II)**) and the appropriate diamines in 2:1 molar ratio. The Schiff base (Fig. 1.5a) was prepared using the *o*-1,2-phenylenediamines and compound **(II)** (Kitaura, et al., 2004). Other Schiff bases (Fig. 1.5b) were prepared from the condensation reaction of 3-formyl-2-hydroxybenzoic with 2:1 molar ratios of 1,2-ethelynediamine (Jiang, et al., 2003) and 2,3-diamino-2,3-dimethylbutane (Fritzsche, et al., 2006), respectively.

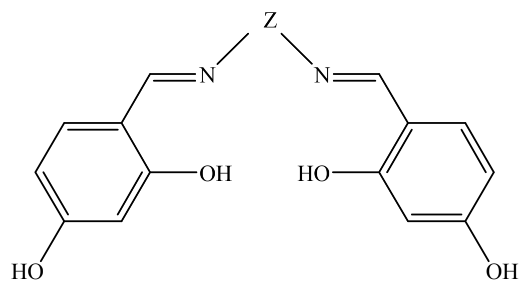


where: (a) Z = *o*-1,2-C_6H_4 , R_1 = H, R_2 = COOH
(b) Z = CH_2CH_2, $C(CH_3)_2C(CH_3)_2$, R_1 = COOH, R_2 = H

Figure 1.5: Examples of tetradentate Schiff bases with carboxyl group substituents.

1.3.3 Schiff Bases Containing Hydroxyl Groups:

Tetradentate Schiff bases containing hydroxyl groups are prepared from condensation of 2,4-dihydroxybenzaldehyde (DHBA) with 1,2-ethylenediamine and 1,2-phenylenediamine in 2:1 molar ratio to produce Schiff bases (a) and (b) shown in Fig. 1.6, respectively (Niasari and Bazarganipour, 2009; Azani, et al., 2009). The closely related Schiff base (Fig. 1.6c) was prepared from the condensation of 2,4-dihydroxybenzaldehyde and 2,3-diamino-2,3-dimethylbutane(Fritzsche, et al., 2006).



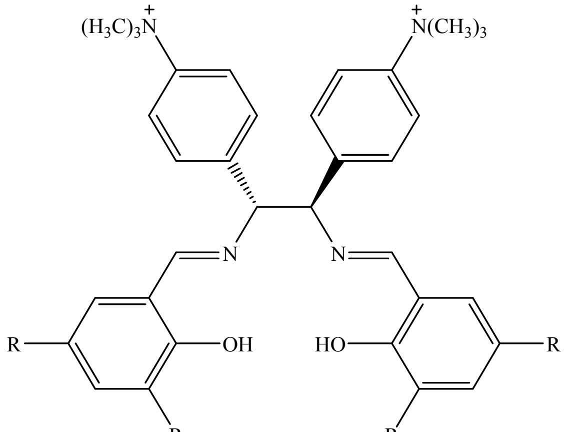
where: (a) Z = CH_2CH_2 (b) Z = o-C_6H_4 (c) Z = $C(CH_3)_2C(CH_3)_2$.

Figure 1.6: Examples of hydroxylated tetradentate Schiff bases

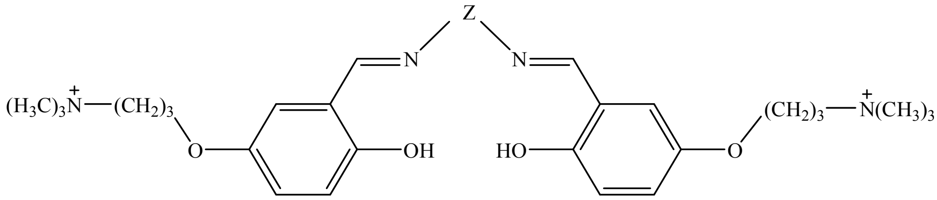
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1.3.4 Schiff Bases Containing Ammonium Groups:

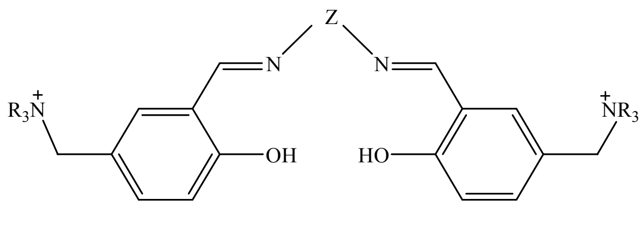
The quaternary ammonium substituents are known of their positive effect on the solubility of salen ligands in water. Two strategies have been used to achieve this objective. The first strategy involves a placement of the quaternary ammonium substituent on the ethylenediamine unit, as shown in (Fig. 1.7a) (Muller, et al., 1999). The second strategy involves a placement of the quaternary ammonium substituents on the salicylaldehydes, shown in (Fig. 1.7b-e) (Muller, et al., 1999; Sato, et al., 1994).



(a) where:R = H, Me, Cl.



where : (b) $Z=CH_2CH_2$,
(c) $Z= o\text{-}C_6H_4$,
(d) $Z=1,2\text{-}C_{10}H_6$.



(e) where: 1: R = Me, $Z = CH_2CH_2$, $o\text{-}C_6H_4$, $2,3\text{-}C_{10}H_6$.
2: R = Et, $Z = CH_2CH_2$, $o\text{-}C_6H_4$.
3: R = Pr, $Z = o\text{-}C_6H_4$.
4: R = Bu, $Z = o\text{-}C_6H_4$.

Figure 1.7: Examples of tetradentate Schiff bases with trialkyl ammonium groups.

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1.3.5 Schiff Bases Containing Phosphonium Groups:

The quaternary phosphonium substituents are also used to enhance the water-solubility of salen Schiff bases and consequently their complexes. Among the water-soluble Schiff bases that have been prepared in the literature is the compound shown in Fig. 1.8: 2,2'-[1,2-ethandiylbis(nitrilomethylidyne)]bis-[4-(triphenylphosphonium)-methyl chloride]bisphenol (Bakherad, et al., 2009).

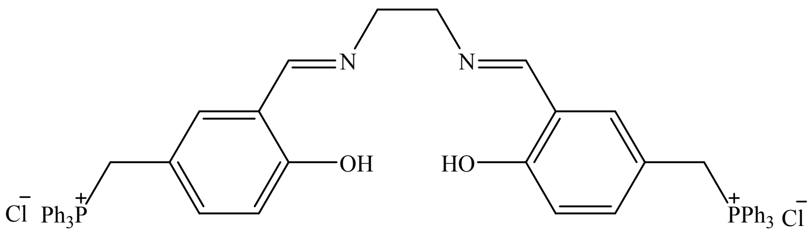


Figure 1.8: An example of phosphoalkylated tetradentate Schiff bases

1.4 Water-Soluble Schiff Bases Derived from 1,2-Diaminocylohexane:

The condensation of Compound **(I)** with *trans*-1,2-diaminocyclohexane affords disodium salt of 3,3'-[*trans*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-4-hydroxybenzenesulfonic acid (Fig. 1.9a) (Qu, et al., 2010).

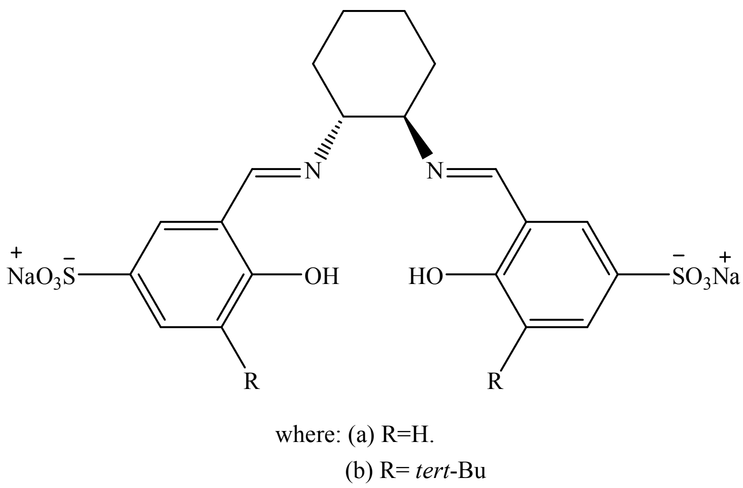
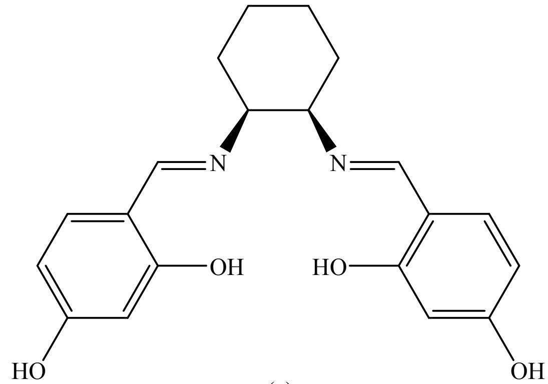


Figure 1.9: Sulfonate - substituted tetradentate Schiff bases derived from DACH.

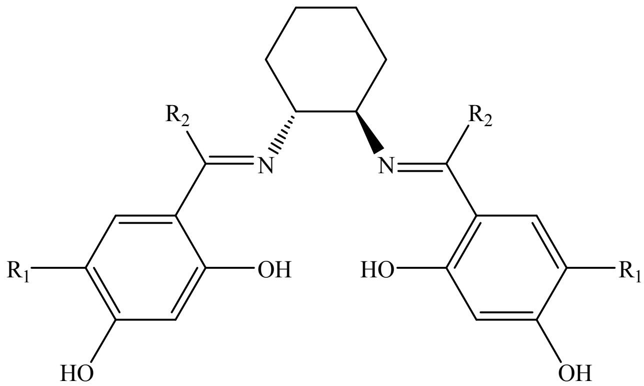
The condensation of 2,4-dihydroxybenzaldehyde (DHBA) with *cis*-1,2-diaminocyclohexane in 2:1 molar ratio affords 4,4'-[*cis*-1,2-cyclohexanediylbis-(nitrilomethylidyne)]bis-1,3-Benzenediol (Fig. 1.10a) (Oliveira, et al., 2009). Similarly, the condensation of *trans*-1,2-diaminocyclohexane with 2,4-dihydroxybenzaldehyde

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(DHBA) and 2,4-dihyroxy-5-nitrophenylmethyl ketone in 2:1 molar ratio affords 4,4'-[*trans*-1,2-cyclohexanediylbis-(nitrilomethylidyne)]bis-1,3-benzenediol (Fig. 1.10b) (Aranha, et al., 2007) and 4,4'-[*trans*-1,2-cyclohexanediylbis(nitriloethylidyne)]bis[6-nitro-1,3-Benzenediol] (Fig.1.10c) (Yaul, et al.,2009), respectively.



(a)



where: (b) $R_1 = R_2 = H$

(c) $R_1 = NO_2$, $R_2 = CH_3$

Figure 1.10: Dihydroxy-substituted tetradentate Schiff base derived from DACH.

The condensation of 4-(N,N)-dialkylaminosalicylaldehyde (alkyl = methyl, ethyl) with *trans*-1,2-diaminocyclohexane in 2:1 molar raio affords 2,2'-[*trans*-1,2-cyclohexanediylbis-(nitrilomethylidyne)]bis-[5-(N,N)-(dialkylamino)phenol](Fig. 1.11a and b) (Bernardo, et al., 1996; Aranha, et al., 2006).

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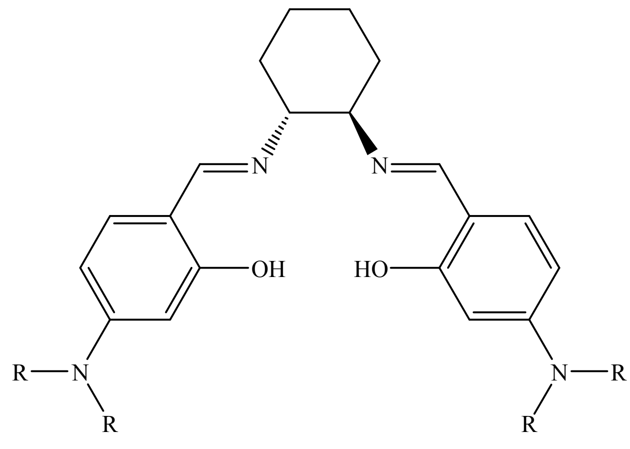


Figure 1.11: Dialkylamino - substituted tetradentate Schiff base derived from DACH**.**

Schiff bases containing quaternary ammonium substituents are prepared from the coupling of quaternary ammonium substituted salicylaldehyde and *trans*-1,2-diaminocyclohexane in 2:1 molar ratio. An example is 3,3'-[*trans*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-[N,N,N-tributyl-5-(1,1-dimethylethyl)-4-hydroxybenzenemethanaminium chloride] (Fig. 1.12) (Chang, et al., 2009).

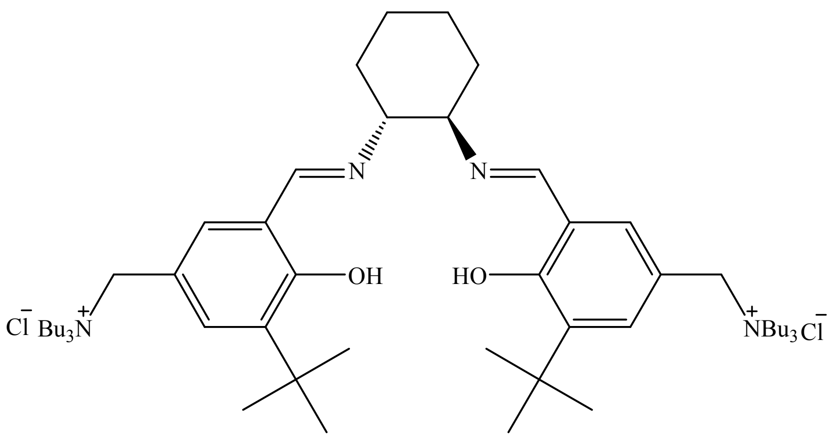


Figure 1.12: Tributylammonium-substituted tetradentate Schiff base derived from DACH**.**

Quaternary phosphonium substituted Schiff base was prepared from the coupling of phosphonium substituted salicylaldehyde and *trans*-1,2-diaminocyclohexane in 2:1 molar ratio (Fig. 1.13). An example is 2,2'-[*trans*-1,2-cyclohexanediylbis(nitrilomethylidyne)]bis-[4-(triphenylphosphonium)methyl chloride-6-(1,1-dimethylethyl)]bisphenol (Chang, et al., 2009).

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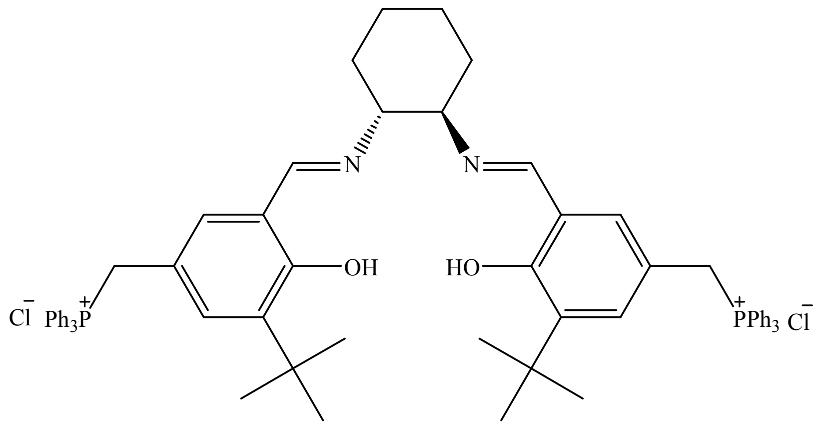


Figure 1.13: Triphenylphosphonium-substituted tetradentate Schiff base derived from DACH.

1.5 Amine Complexes of Platinum as Anticancer Drugs:

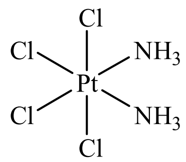
1.5.1 Historical Background:

The first platinum complex reported with cytostatic activity is *cis*-diamminedichloroplatinum(II) (known as cisplatin) and it is one of the most widely used anticancer drugs today. The cytostatic activity of cisplatin was first reported by Barnett Rosenberg and coworkers in 1965, while examining photographs of mitosis (cell undergoing division) (Rosenberg, et al., 1970). Rosenberg noticed a similarity between the mitotic spindles (lines results upon cell division) and the force lines in electric and magnetic fields. These observations raised the question in Rosenberg's mind as to whether or not electric fields affect cell division. He therefore decided to examine the effects of electric fields on cells cultured in laboratory. He used the platinum electrodes to subject *E. Coli* bacteria to the electric fields. Unexpected results were found, the cells stopped dividing but they started to elongate to form long filaments about 300 times their normal size (Rosenberg, et al., 1965).

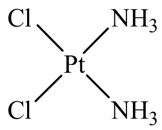
In other words, cell division / replication was inhibited but not the cell growth. Then, Rosenberg and coworkers tried to determine the exact reason by varying one experimental parameter at a time. The conclusions of this experiment were that the application of electric current was not itself responsible for the observed inhibition of

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cell division but that the electric current led to formation of new chemical species caused that inhibition. The chemical species formed were: *cis*-diamminetetrachloroplatinum(IV) $[Pt(NH_3)_2Cl_4]$ (Fig. 1.14a) and *cis*-diammine-dichloroplatinum(II) $[Pt(NH_3)_2Cl_2]$ (Fig. 1.14b) (Rosenberg, et al., 1965; Abu-Surrah and Kettunen, 2006). The latter complex showed higher activity and developed as anti-cancer drug with the commercial name cisplatin (Rosenberg, et al., 1970).



(a)



(b)

Figure 1.14: (a) *cis*-diamminetetrachloroplatinum(IV)
(b) *cis*-diamminedichloroplatinum(II)

1.5.2 Platinum Complexes as Anti-Cancer Drugs:

The first compound used in cancer chemotherapy, is *cis*-diammine-dichloroplatinum(II) or cisplatin, and was first given to cancer patients in 1971. It became ready for treatment of cancer patients in 1978. Since then, extensive research has continued in this area (Lebwohl and Canetta, 1998).

Among the huge number of platinum complexes prepared, five are currently approved: *cis*-diamminedichloroplatinum(II) (cisplatin) (Fig. 1.14b), *cis*-cyclobutyl-1,1-dicarboxylatodiamineplatinum(II) (carboplatin) (Fig. 1.15a), *cis*-oxalato-*trans*-*l*-1,2-diaminocyclohexaneplatinum(II) (oxaliplatin) (Fig. 1.15b), *cis*-glycolato-diammineplatinum(II) (nedaplatin) (Fig. 1.15c) and *cis*-lactatodiamminomethylcyclo-butaneplatinum(II) (lobaplatin) (Fig. 1.15d). Moreover, a few more remain under clinical investigations (Florea and Büsselberg, 2011; Zhang, et al., 2010).

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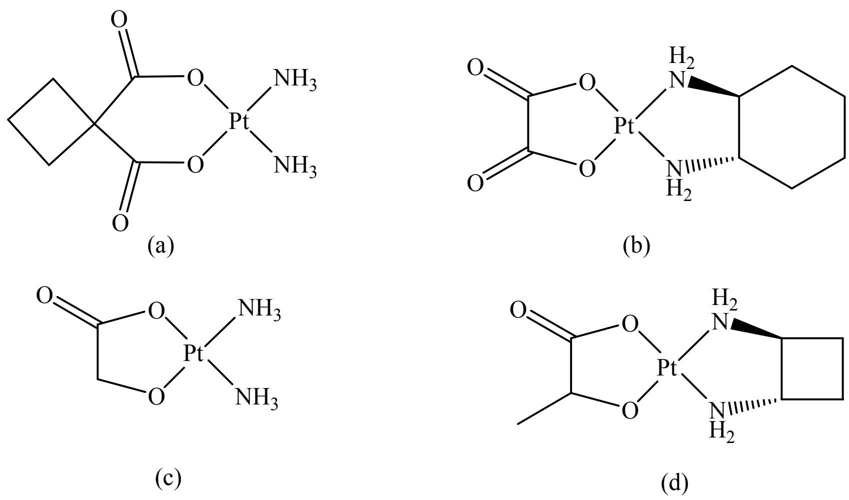


Figure 1.15: Structures of (a) carboplatin (b) oxaliplatin (c) nedaplatin (d) lobaplatin.

In addition to that, based on the clinical trials, a set of structure/activity relationships (SAR) were assigned for platinum chemotherapy drugs and are approved by certain researchers, which are summarized as follows: 1) the complex should have a zero net charge; 2) the complex should have two good leaving groups such as Cl^{-} or other similar ligands or one bidentate leaving group such as SO_4^{2-}, citrate, oxalate and other carboxyl groups; 3) the complex should not contain free OH^{-} ligands, as these make the complex highly toxic; 4) the complex should have other non-leaving ligands which are inert, preferably amine or ammonia ligands, either monodentate or bidentate in which they have at least one NH group (Zhang, et al., 2009; Abu-Surrah, 2007).

1.5.3 Mechanism of Action:

The mechanism of action requires the binding of the anti-cancer drug on the nitrogen nucleotides present on DNA which will stop the DNA replication and thus stops cell division. Accordingly, cisplatin is expected to bind to DNA and inhibits the replication in the cancer cells. But before the binding mechanism of the cisplatin, substitution reactions of coordinated chloride ligands are the key chemistry in reactions of cisplatin in a human cell. The presence of suitable concentration of chloride ion inside blood stream reduces the probability of hydrolysis of cisplatin and thus cisplatin becomes stable for a certain period of time (Lawrance, 2009).

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After the tour of cisplatin inside the body, it crosses the cytoplasmic membrane of a cell and meets a much reduced chloride concentration which leads to a series of hydrolysis reactions, forming at first the aqua complex [$PtCl(NH_3)_2(OH_2)$] (Kasparkova, et al., 2003).

As the Pt-O is labile and easily broken, this enhances the binding of the vacant site of the complex to N atom present on one of the nitrogen bases of DNA (cytosine, guanine, adenine and thymidine). Unfortunately, cisplatin is not regiospecific, that is, it cannot distinguish the tumor cells from other cells. Furthermore, it can participate in coordination with sulfur-containing groups and other functionalities that lead finally to its inactivation (Reedijk, 1987; Kasparkova, et al., 2003); the pathways of cisplatin are summarized in Fig. 1.16.

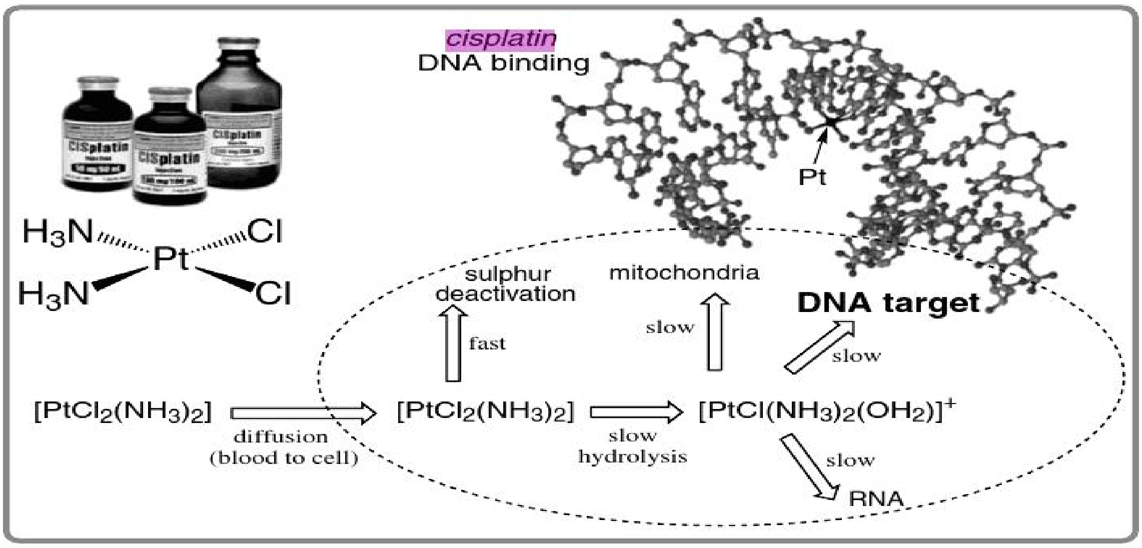


Figure 1.16: The drug cisplatin, its reaction pathways in the cell and an example of coordination to DNA, leading to distortion of the double helix.

The cationic aqua complexes formed upon initial chloride hydrolysis (particularly [$Pt(NH_3)_2(OH_2)_2]^{2+}$) enhance the activity of the drug as an agent due to an ionic attraction to the negatively-charged DNA helix, which has an anionic phosphate groups. There is a strong belief that the structural changes arising from coordination of N-donor DNA bases in place of water ligands are the key to activity of cisplatin. In addition, the cisplatin can bind to other proteins and biomolecules, sometimes together

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with binding to DNA. Therefore, the hydrolysis of both chloride ion ligands is necessary. Possible modes of binding are illustrated in Figure 1.17 (Lawrance, 2009).

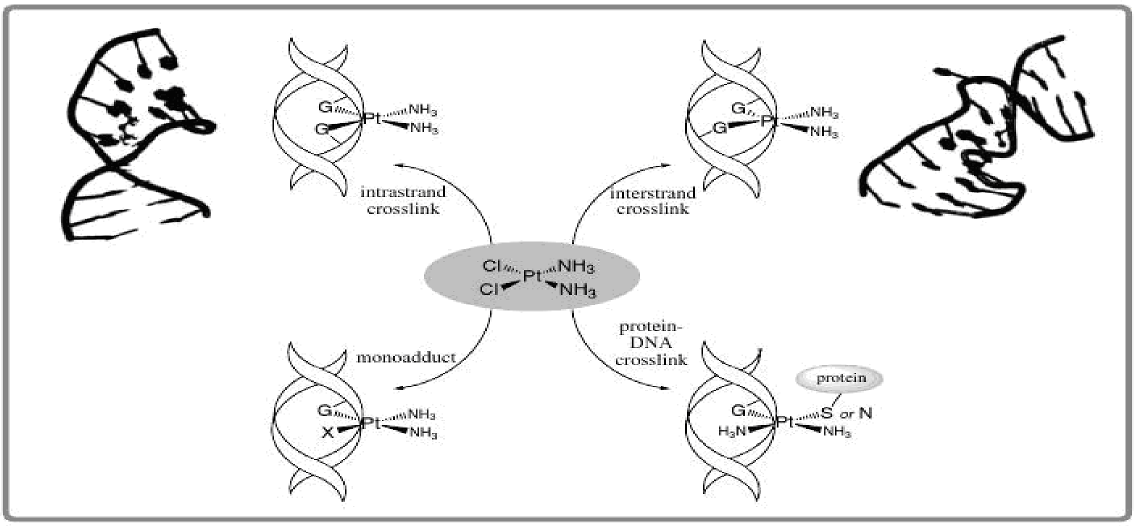


Figure 1.17: Various modes of coordination of the platinum(II) drug cisplatin to bases in DNA strands, following initial chloride hydrolysis; a guanine N-donor (G) is favored.

Cisplatin can form intrastrand crosslinks between adjacent bases, preferring two guanine bases (Kasparkova et al., 2003). Now it is obvious why *trans*-diamminodichloroplatinum(II), transplatin, is inactive towards inhibition of cell propagation because the previous mechanism requires two adjacent vacant sites which are available in case of cisplatin and cisplatin analogues (Lawrance, 2009).

1.5.4 Cisplatin:

Cisplatin is one of the most effective chemotherapeutic drugs used for the treatment of a variety of cancers, especially testicular, ovarian, head, neck, bladder cancers and other solid tumors (Kelland, et al., 1999). Despite its activity in many cancers, cisplatin is ineffective in others e.g. leukemia (blood cancer), renal (kidney) and gastrointestinal (stomach and intestine, and sometimes refers to all the structures from the mouth to the anus) cancers. However, the drug's clinical usage is restricted by both toxicological and especially tumor resistance considerations which can be either intrinsic (i.e. present at the onset of treatment) or acquired (i.e. occurs during chemotherapy) (Abu-Surrah, 2007).

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The major toxicity limitations of cisplatin are: kidney toxicity (most notable), vomiting, peripheral neuropathy (damage to nerves of the peripheral nervous system), and myelotoxicity (Inhibitory, depressant, or destructive to a component of bone marrow) (Abu-Surrah and Kettunen, 2006). Both toxicological and tumor resistance considerations of cisplatin led the researchers to prepare new alternative platinum complexes which have better activity, lower toxicity and obey the SAR. Great efforts and work have been made to develop and synthesize new derivatives or analogues of cisplatin with improved pharmacological properties (Zhang, et al., 2009). Examples of cisplatin analogues are shown in Fig. 1.18 (Kelland, et al., 2009)

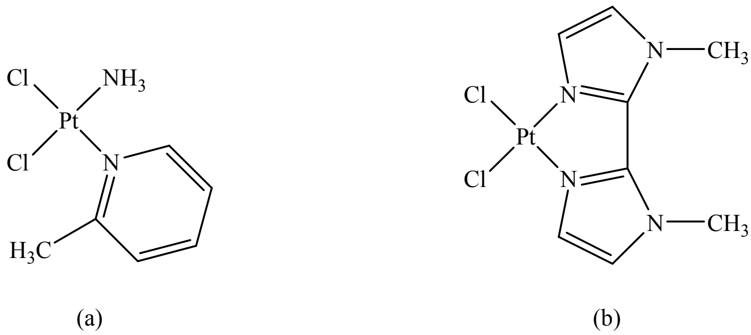


Figure 1.18: Cisplatin analogues: (a) Amminedichloro-(2-methylpyridine)platinum(II) (b) Dichloro-(1,1'-dimethyl-2,2'-bi-1H- imidazole-N3,N3')-platinum(II).

1.5.5 Second Generation of Platinum Complexes: Carboplatin Analogues Complexes:

A new series of platinum complexes have been prepared by replacing the two chloro- ligands in cisplatin either with chelating carboxylate, oxalate, sulfate or glycolate. Changing the leaving group (Cl^-) is the main feature of the second generation of platinum compounds (Yonezawa and Inui, 2011).

A lot of carboplatin (*cis*-cyclobutane-1,1-dicarboxylatodiammineplatinum(II)) analogues containing cyclobutane ring have been prepared in order to improve the carboplatin characteristics. Among these compounds: cyclobutane-1,1-dicarboxylato-[2,2-bis(aminomethyl)-1,3-propandiol]platinum(II) (Fig. 1.19a), (cyclobutane-1,1-dicarboxylatotetrahydro-4Hpyran-4,4-dimethylamineplatinum(II) (Fig. 1.19b) (Bitha, et

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al., 1989), cyclobutane-1,1-dicarboxylato-2-aminomethylpyrrolidineplatinum(II) (Fig. 1.19c), *cis*-glycolatodiamineplatinum(II) (Fig. 1.19d) (Kobayashi et al., 1991), *cis*-lactatodiaminomethylcyclobutaneplatinum(II)(Fig. 1.19e), [2-(1-methylethyl)-1,3-dioxolane-4,5-dimethanamine-N,N'][propanedioato-O,O'] platinum(II) (Fig. 1.19f) (Zhang, et al., 2009), *cis*-1,2-propylendiammine(cyclobutane-1,1-dicarboxylato)-platinum(II) (Fig. 1.19g) and *cis*-isobutylendiammine(cyclobutane-1,1-dicarboxylato)-platinum(II) (Fig. 1.19h) (Kojic, et al., 2005).

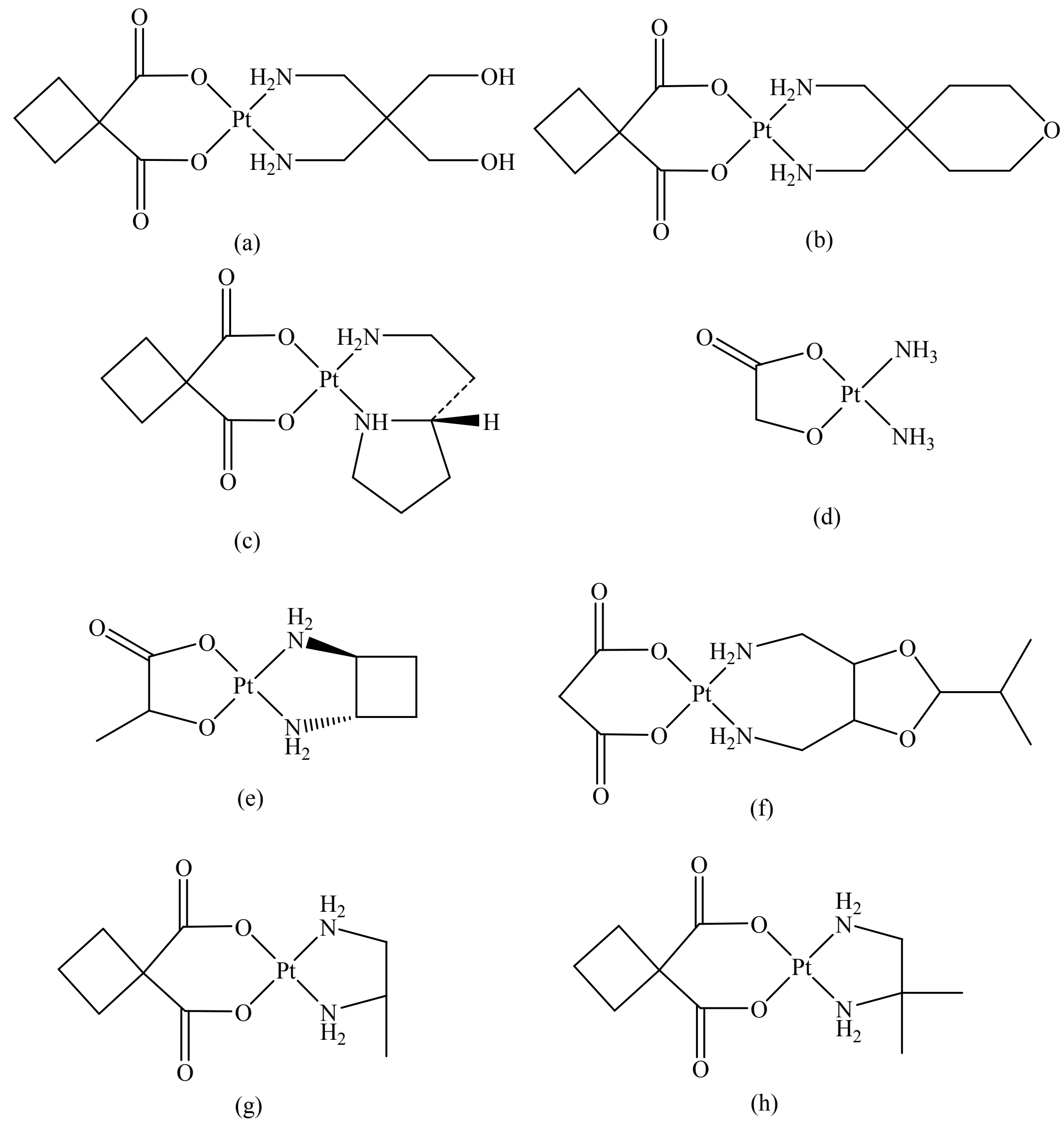


Figure 1.19: The carboplatin analogues.

Although carboplatin $[(NH_3)_2Pt(C_4H_6O_4)]$ (Fig. 1.15a) is the most active compound of the second generation of platinum complexes, cisplatin is considered to be

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a better compound compared to carboplatin in terms of therapeutic efficacy across the several types of tumors and the toxicity profile (Lokich, 2001).

1.5.6 Third Generation of Platinum Complexes: Complexes Containing Chiral 1,2-Diaminocylohexane:

Interestingly, the compounds of 1,2-diaminocyclohexane have shown a higher activity against mice leukemias, lack of cross-resistance and less renal (kidney) toxicity than cisplatin (Burchenal, et al., 1979). For example, it was found that [*cis*-1R,2R-(DACH)$PtCl_2$] (Fig. 1.20a), was the most active and the least toxic on kidneys among its analogues. Unfortunately, this complex is found to be water-insoluble (Abu-Surrah, 2007).

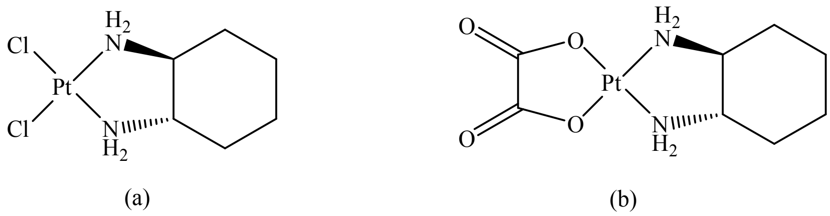


Figure 1.20: (a) *cis*-1R,2R-(DACH)$PtCl_2$ (b) oxaloplatin.

Compared with the previous generations the relatively water-soluble complex, oxaliplatin, ($Pt(C_2O_4)$[(1*R*, 2*R*)-DACH]) (Fig. 1.20b) is the most effective. The good water-solubility of this complex led the researchers all over the world to prepare structurally related platinum complexes (Fig. 1.21). Some of these complexes had already undergone clinical trials aiming to find a more active and less toxic target complex (Al-Allaf, et al., 2009).

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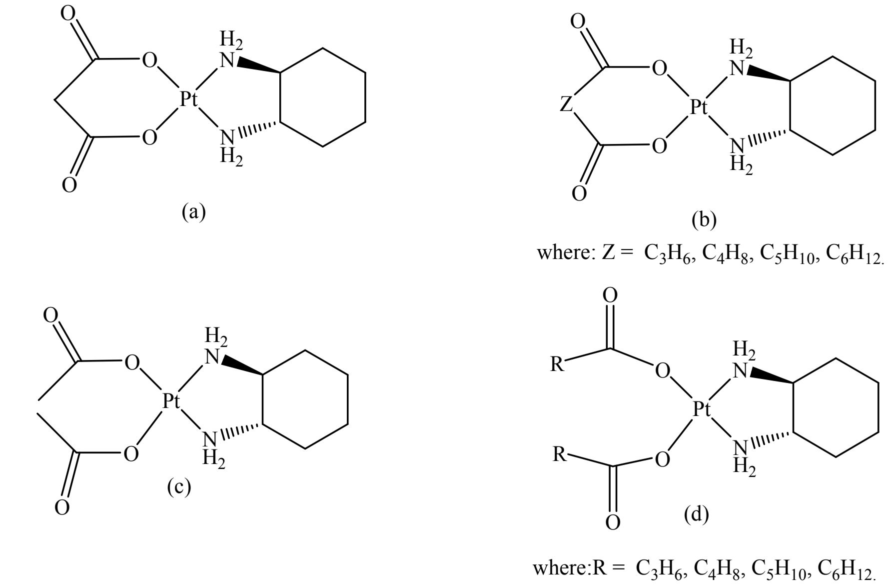


Figure 1.21: Structures of oxaliplatin analogues: (a) *cis*-propanedioato-*trans*-*l*-1,2-diamino-cyclohexaneplatinum(II) (b) *cis*-cycloalkane-1,1-dicarboxylato-*trans*-*l*-1,2-diamino-cyclohexaneplatinum(II) (c) *cis*-bis(acetate)-*trans*-*l*-1,2-diaminocyclohexane-platinum(II) (d) *cis*-bis(cycloalkanecarboxylato)-*trans*-*l*-1,2-diaminocyclohexane-platinum(II).

All complexes in Fig 1.21 were examined *in vitro* (outside human) against set of tumor cell lines and the results were compared with oxaliplatin. However, these complexes appeared to have less antitumor-activity (Al-Allaf, et al., 2009).

Moreover, oxaliplatin is a distinctive from both cisplatin and carboplatin due to higher activity and non-cross-resistance with some platinum-resistant experimental tumor systems (Lokich, 2001).

In terms of clinical activity, oxaliplatin is the first platinum complex that demonstrated activity in colon and ovarian cancers. By comparison with cisplatin, oxaliplatin have greater chemical stability and slower hydrolysis (Lebwol and Canetta, 1998).

In summary, cisplatin, carboplatin and oxaliplatin are the most active agents towards several types of cancer, with preferential activity for oxaliplatin. Although the above three complexes are most active anticancer agents, the intrinsic resistance in cancer cell line led to global search for more effective and less toxic platinum-based

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anticancer drugs (Yu, et al., 2006). The search pursues different strategies that includes the changing the coordination of nitrogen ligands (Kasparkova, et al., 2003), altering the leaving groups (Bernhardt, et al., 2004) or replacing platinum(II) by other metal ions such as platinum(IV) (Hall, et al., 2007), palladium(II) or nickel(II) (Casas, et al., 2008; Abu-Surrah, 2007).

In addition to that, some of the platinum complexes that have been synthesized and evaluated for their anticancer activity suffer from low solubility in water (Abu-Surrah, 2007). Accordingly, much work was directed towards the synthesis water-soluble platinum complexes (Song, et al., 2002) and in specific water-soluble platinum complexes having DACH bidentate ligand (Gandolfi, et al., 1987; Kidani, 1990).

The importance of solubility of platinum complexes is to facilitate the motion of the complex inside the blood stream, reduce sticking with lipophilic places inside the body and reduce the accumulation of platinum inside the body after the possible hydrolysis in the body fluids.

1.6 Platinum Complexes of Water-Soluble Schiff Base Ligands:

To our knowledge, no platinum complexes with water-soluble Schiff base ligands have been prepared in the literature.

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1.7 Objectives:

The purpose of this work is to synthesize new water-soluble platinum(II) complexes closely related to oxaliplatin but with higher solubility in water. In this work the amine ligand and the groups are built-in parts of the Schiff base ligands. The Schiff bases will be prepared from the condensation of 1,2-diaminocylcohexane and substituted salicylaldehyde in 2:1 molar ratios. The substituents are chosen in a way to increase the hydrophilic character of the Schiff bases and consequently the platinum complexes. The salicylaldehydes are prepared to bear one of the following groups: sulfonyl, carboxyl, hydroxyl or dimethylamino groups. With their close similarity to oxaliplatin and their high water-solubility, the proposed complexes are expected to show good activity and less toxicity.

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2. EXPERIMENTAL

2.1 Chemicals and Materials:

Methanol, aniline and barium chloride dihydrate were purchased from Merck, Germany. Ethanol was purchased from Labchem, UK. N,N-Dimethylformamide, dimethylsulfoxide, sodium hydrogen carbonate (A.R), sodium hydroxide (A.R) and glacial acetic acid were purchased from SDS, France. Hydrochloric acid was purchased from M TEDIA, USA. Sulfuric acid was purchased from GCC, U.K. 3-*N,N*-dimethylaminophenol, phosphoryl chloride, potassium tetrachloroplatinate, salicylaldehyde, *p*-hydroxybenzoic acid, mixture of *cis*- and *trans*- isomers of 1,2-diaminocyclohexane 99% and chloroform were purchased from Across, Belgium. Sodium and magnesium sulfate anhydrous were purchased from Scharlau, Spain. Sodium borohydride was purchased from Thomas Baker, India. Sodium carbonate anhydrous was purchased from Lonover, England. Nickel chloride hexahydrate was purchased from VWR, Belgium.

2.2 Physical Measurements:

The IR spectra were recorded, as KBr discs, on Nicolet impact-400 FT-IR spectrophotometer. The NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer using TMS as internal reference. Melting points were determined with Fisher-Johns melting point apparatus and were uncorrected.

2.3 Purification of Chemical Reagents:

Solvents were dried according to literature procedures (Armarego and Perrin, 2000).

2.3.1 Dry Ethanol:

5.00 g of clean dry magnesium turnings and 0.500 g of iodine were placed in a 2.0 L round bottom flask, followed by addition of 50.0 -75.0 mL of absolute ethanol, the mixture was warmed until a vigorous reaction occurs. When this subsides, heating

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was continued until all the magnesium was converted to magnesium ethoxide and the brown color disappeared. Absolute ethanol was added up to 1L and refluxed for 1 hour, then distilled off.

2.3.2 Dry Methanol:

Methanol was dried using the same procedure in section 2.3.1 but replacing absolute ethanol by absolute methanol.

2.3.3 Dry Dimethylsulfoxide (DMSO):

500. mL of dimethylsulfoxide was mixed with 50.0 g of barium oxide and then the mixture was stirred for 24 hours then filtered. The filtrate was fractionally distilled under reduced pressure.

2.3.4 Dry N,N-Dimethylformamide (DMF):

500. mL of N,N-dimethylformamide was mixed with 50.0 g of sodium sulfate, and then the mixture was stirred for 24 hours then filtered. The filtrate was distilled under reduced pressure.

2.4 Preparation of the Starting Materials:

2.4.1 Separation of *cis*-1,2-Diaminocyclohexane (*cis*-DACH) from a Mixture of *cis*- and *trans*-1,2-Diaminocyclohexane Via Selective Formation of Nickel (II) Complex.

The *cis-trans* diastereomers of 1,2-diaminocyclohexane were separated following literature procedure (Saito and Kidani, 1976) with some modifications.

A solution of 1,2-diaminocyclohexane mixture (DACH) (25.0 g, 220. mmol) in methanol (160. mL) was added to a solution of $NiCl_2.6H_2O$ (26.0 g, 110. mmol) in methanol (440. mL). The mixture was stirred for 2 hours at room temperature to give a yellow precipitate. This precipitate was collected, washed with methanol and dried at 50 °C in vacuum to give 12.0 g (61.2 %) of the yellow nickel complex, Ni(*cis*-

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$DACH)_2Cl_2$. [The mother liquor was kept for further work to isolate the Ni[(*trans*-$DACH)_2(H_2O)_2]Cl_2$].

2.4.1.a Preparation of *cis*-1,2-Diaminocyclohexane Dihydrochloride (*cis*-DACH.2HCl):

A sample of Ni(*cis*-$DACH)_2Cl_2$ (10.0 g, 27.9 mmol) was decomposed carefully by adding 4.00 M H_2SO_4 (13.95 mL, 55.8 mmol), and the solvent was removed completely under reduced pressure. Absolute ethanol (40. mL) was added to disperse the residue leading to the formation of a white precipitate. The precipitate was filtered off and washed thoroughly with dry methanol (3 × 50. mL) to get rid of the blue color. The precipitate was dried at 45 °C in vacuum for 3 hours to give 8.70 g (73.4 %) of *cis*-DACH.H_2SO_4. Then, a solution of *cis*-DACH.H_2SO_4 (8.00 g, 38.0 mmol) in deionized water (180. mL) was added to a solution of $BaCl_2.2H_2O$ (9.20 g, 38.0 mmol) in deionized water (50. mL). The white precipitate formed was digested in water bath at 80 °C for 3 hours. The mixture was filtered through 3 filter papers. The water in the filtrate was evaporated under reduced pressure. Dry ethanol (20. mL) was added to the residue, and then evaporated under reduced pressure to remove the traces of water. The precipitate was collected and dried at 50 °C in vacuum for 5 hours to give 6.10 g (85.8 %) of *cis*-DACH.2HCl.

2.4.1.b Preparation of *trans*-1,2-Diaminocyclohexane Dihydrochloride (*trans*-DACH.2HCl):

The filtrate from step 2.4.1 which contains Ni[(*trans*-$DACH)_2(H_2O)_2]Cl_2$ was acidified with 6.00 M HCl (35.0 mL). Then the pH was adjusted to 4.20 - 4.50 using 15% NaOH. The violet deposit was filtered-off, washed thoroughly with deionized water and dried at 50 °C in vacuum for 5 hours to give 5.90 g (40.3 %) of Ni[(*trans*-$DACH)_2(H_2O)_2]Cl_2$. After that, a sample of Ni[(*trans*-$DACH)_2(H_2O)_2]Cl_2$ (5.00 g, 12.7 mmol) was decomposed carefully by adding 6.00 M HCl (8.70 mL, 50.8 mmol). Water

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was removed completely from the solution under reduced pressure. The white precipitate was washed with minimum amount of cold methanol. The precipitate was filtered off and dried at 50 °C in vacuum for 3 hours to give 4.47 g (94.1 %) of *trans*-DACH.2HCl.

2.4.2 Preparation of the Sodium Salt of Salicylaldehyde-5-sulfonic Acid, (I):

This compound was prepared through 3 steps as shown in the following:

2.4.2.a Preparation of N-Phenylsalicyldimine:

The title compound was prepared following literature procedure (Khera, 1983).

Freshly distilled colorless aniline (22.3 g, 240. mmol) in dry ethanol (150.0 mL) was added dropwise under vigorous stirring to a solution of salicylaldehyde (24.4 g, 200. mmol) in absolute ethanol (100. mL) over a period of 1 hour, the solution color turned to yellow during the addition. The solution was refluxed for 2 hours and then cooled to 0.0 °C to afford the precipitation. The yellow precipitate was filtered off and dried at 25.0 °C in vacuum for 3 hours to give 35.1 g (95.4 %) of N-phenylsalicyldimine.

2.4.2.b Preparation of N-Phenylsalicyldimine-5-sulphonic Acid :

The title compound was prepared following literature procedure (Berry et al., 1982).

N-phenylsalicyldimine (17.7 g, 90.0 mmol) was added to concentrated sulfuric acid (47.5 mL, 87.4 g, 892. mmol) and the mixture was kept at a temperature of 100.0 ± 5.0 °C with occasional stirring for 2 hours. The solution's color turns to yellowish-brown. After cooling to room temperature, the solution was added slowly to crushed ice-water (600. mL) with vigorous stirring, the color turned to bright yellow. The mixture was reheated until all solids had dissolved (between 75.0 - 80.0 °C). The solution was then allowed to cool to room temperature; the yellow solid was filtered off

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and dried at 45 °C in vacuum for 8 hours to give 23.3 g (93.7%) of N-phenylsalicyldimine-5-sulphonic acid.

2.4.2.c Preparation of Sodium Salt of Salicylaldehyde-5-sulfonic Acid, (I):

The title compound was prepared following literature procedure (Botsivali et al., 1985).

N-phenylsalicylaldimine-5-sulphonic acid (20.0 g, 72.1 mmol) was added to an aqueous solution (150.0 mL) of anhydrous Na_2CO_3 (13.8 g, 130. mmol) and the solution was then boiled vigorously to remove aniline (heat must be raised gradually). Aniline was efficiently removed by simple distillation of the solution with occasional addition of hot water to compensate for the amount of distilled water. Distillation continued till complete removal of aniline (~ 3 hours). The solution was then cooled and glacial acetic acid (few milliliters) was slowly added to bring the pH to about 5.0. Ethanol (120. mL) was added to precipitate the product. The solution was cooled to 0.0 °C and the yellow solid was filtered off, recrystallized from water-ethanol (1:1) and finally dried at 45 °C in vacuum for 2 hours to give 14.2 g (87.8 %) of **(I)**.

2.4.3 Preparation of 3-Formyl-4-hydroxybenzoic Acid, (II):

The title compound was prepared following literature procedure with some modifications (Wynberg, 1954).

p-Hydroxybenzoic acid (27.60 g, 200. mmol) was added slowly with vigorous stirring to a hot solution of NaOH (100. g, 2.50 mol) in water (180. mL). The acid was completely dissolved in the sodium hydroxide solution. The solution was allowed to cool to about 70.0 °C. Chloroform (50.0 mL) was added dropwise to the stirred solution at a rate to keep the temperature in the range 70.0-80.0 °C. The solution was further stirred at the same temperature for 24 hours. The mixture was cooled and then acidified with 5.00 M H_2SO_4 to produce an off-white precipitate. The precipitate was filtered off,

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dried at 50 °C in vacuum for 5 hours and then recrystallized 4 times from water to give 3.1 g (9.33%) of **(II)**.

2.4.4 Preparation of 4-(N,N-Dimethylamino)salicylaldehyde,(III):

The title compound was prepared following literature procedure with some modifications (Flašík, et al., 2009).

A solution of recrystallized 3-(*N,N*-dimethylamino)phenol (14.4 g, 105. mmol) in dry N,N-dimethylformamide (DMF) (20.0 mL) was added dropwise to a Vilsmeier-Haack adduct [prepared from mixing $POCl_3$ (19.2 mL, 210. mmol) and dry DMF (39.0 mL, 508. mmol) at -5.0 °C for 30 minutes]. The reaction mixture was stirred at room temperature for 30 minutes, and then at 85.0-90.0 °C for 4 hours. Finally, it was stirred at room temperature overnight. The reaction mixture was poured into crushed ice (600. g) and the solution was neutralized to litmus with saturated solution of Na_2CO_3 (~130 mL). The precipitate was left for 2 hours, filtered off, washed thoroughly with water and dried at 25 °C in vacuum for 8 hours to give 9.70 g (55.9 %) of **(III)**.

2.5 Preparation of the Schiff Base Ligands:

2.5.1 Schiff Bases Derived from *cis*-1,2-Diaminocyclohexane (*cis*-DACH):

2.5.1.a Preparation of Disodium Salt of 3,3'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]bis-4-hydroxybenzenesulfonic Acid, (IV):

A small piece of sodium metal (0.644 g, 28.0 mmol) was added with vigorous stirring to dry ethanol (25.0 mL) to produce sodium ethoxide. Stirring at room temperature was continued until complete reaction of sodium. *cis*-DACH.2HCl (2.62 g, 14.0 mmol) was added with good stirring to the sodium ethoxide solution. After the addition was complete, the mixture was further stirred at room temperature for

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30 minutes. The mixture was filtered and the filtrate containing *cis*-DACH was kept to the following step.

To a suspension of **(I)** (6.28 g, 28.0 mmol) in dry ethanol (600. mL), water (~ 3 mL) was dropwise added to dissolve the salt. The filtrate containing *cis*-DACH (14.0 mmol) was then added dropwise to the stirred solution at 60.0 °C. The mixture was further stirred at 60.0 °C for 1 hour and then cooled in an ice bath to afford precipitation. The precipitate was filtered off, washed with ethanol, diethylether, recrystallized from aqueous ethanol and then dried at 40 °C in vacuum for 2 hours to give 5.80 g (78.7 %) of **(IV)**.

2.5.1.b Preparation of 4,4'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethyl-idyne)]bis-1,3-benzenediol, (V):

The title compound was prepared following literature procedure with some modifications (Aranha et al., 2007).

An ethanolic solution (25.0 mL) containing (37.0 mmol) of *cis*-DACH was prepared as in 2.5.1.a and kept for the next step.

A sample of 2,4-Dihydroxybenzaldehyde (DHBA) (10.2 g, 74.0 mmol) in dry ethanol (100. mL) was stirred well until the solid just dissolved. The filtrate containing *cis*-DACH (37.0 mmol) was then added dropwise to the stirred solution at 60.0 °C. The mixture was further stirred at 60.0 °C for 1 hour and then cooled. The precipitate was filtered off, washed with ethanol and then dried at 40 °C in vacuum for 2 hours to give 11.20 g (85.4 %) of **(V)**.

2.5.1.c Preparation of 3,3'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethyl-idyne)]bis-4-hydroxybenzoic Acid, (VI):

An ethanolic solution (15.0 mL) containing (7.50 mmol) of *cis*-DACH was prepared as in 2.5.1.a and kept for the next step.

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A sample of **(II)** (2.49 g, 15.0 mmol) in dry ethanol (50. mL) was stirred well until the solid just dissolved. The filtrate containing *cis*-DACH (7.50 mmol) was then added dropwise to the stirred solution at 60.0 °C. The mixture was further stirred at 60.0 °C for 2 hours and then cooled to room temperature. The precipitate was filtered off, washed with methanol, acetone and then dried at 40 °C in vacuum for 2 hours to give 2.50 g (81.2 %) of **(VI)**.

2.5.1.d Preparation of 2,2'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethyl-idyne)]bis-[5-(N,N)-(dimethylamino)phenol], (VII):

An ethanolic solution (15.0 mL) containing (5.51 mmol) of *cis*-DACH was prepared as in 2.5.1.a and kept for the next step.

A sample of **(III)** (1.82 g, 11.0 mmol) in dry ethanol (50. mL) was stirred well until the solid just dissolved. The filtrate containing *cis*-DACH (5.51 mmol) was then added dropwise to the stirred solution. The mixture was further stirred at 80.0 °C for 9 hours and at room temperature overnight. The yellow precipitate was filtered off, washed with cold methanol and then dried at 40 °C in vacuum for 2 hours to give 1.13 g (50.2 %) of **(VII)**.

2.5.1.e Attempts to Prepare the Reduced Schiff Base of 2,2'-[*cis*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]bis[5-(N,N)-dimethylamino)phenol] [Reduced form of (VII)]:

A sample of $NaBH_4$ (0.151 g, 4.00 mmol) was added in small portions with vigorous stirring to a solution of **(VII)** (0.408 g, 1.00 mmol) in methanol (15. mL). The solution became colorless after 15 minutes. Stirring was continued at room temperature for 4 hours. Solvent was evaporated under reduced pressure. Water (25. mL) was added to the reaction mixture and was stirred vigorously for 2 hours at room temperature. The white-product was filtered, washed and dried in vacuum oven at 25 °C in vacuum for 5 hours to give 0.220 g of reduced Schiff base of **(VII)**.

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2.5.2 Schiff Bases Derived from *trans*-1,2-Diaminocyclohexane (*trans*-DACH):

2.5.2.a Preparation of Disodium Salt of 3,3'-[*trans*-1,2-Cyclohexane diylbis(nitrilomethylidyne)]bis-4-hydroxybenzenesulfonic Acid, (VIII):

The title compound was prepared following literature procedure with some modifications (Qu et al., 2010).

It was prepared as in section 2.5.1.a using *trans*-DACH and the aldehyde **(I)**. The yield was 5.50 g (74.6%) of **(VIII)**.

2.5.2.b Preparation of 4,4'-[*trans*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]bis-1,3-benzenediol, (IX):

The title compound was prepared following literature procedure with some modifications (Aranha et al., 2007).

It was prepared as in section 2.5.1.b using *trans*-DACH and DHBA. The yield was 11.30 g (86.2 %) of **(IX)**.

2.5.2.c Preparation of 2,2'-[*trans*-1,2-Cyclohexanediylbis(nitrilomethylidyne)]bis-[5-(N,N)-(dimethylamino)phenol], (X):

The title compound was prepared following literature procedure with some modifications (Aranha et al., 2007).

It was prepared as in section 2.5.1.d using *trans*-DACH and aldehyde **(III)**. The yield was 1.40 g (62.2 %) of **(X)**.

2.6 General Procedure for the Preparation of the Platinum Complexes:

All complexes were prepared following literature procedure (Che, et al., 2010) with some modifications.

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2.6.1 Preparation of Platinum Complexes with Schiff Bases Containing *cis*-DACH Ligands:

A sample of the Schiff base ligand (0.500 mmol) was suspended in methanol (15.0 mL). To the mixture, sodium acetate (0.082 g, 1.00 mmol) was added. Then a solution of K_2PtCl_4 (0.207 g, 0.500 mmol) in DMSO (2.0 mL) was dropwise added. The mixture was stirred at 70.0 °C for 15 hours and then allowed to cool to room temperature. Methanol (10.0 mL) was added to precipitate the product. The precipitate was filtered, washed with methanol and dried at 50 °C in vacuum for 2 hours to give the platinum complex.

2.6.1.a Preparation of Sodium [3,3'-[*cis*-1,2-Cyclohexanediyl-bis[(nitrilo-κN)methylidyne]]bis[4-(hydroxy-κO)benzenesulfonato]]-platinate(II), (XI):

A sample of the Schiff base ligand **(IV)** (0.500 mmol) was suspended in methanol (15.0 mL). To the mixture, sodium acetate (0.082 g, 1.00 mmol) was added. Then a solution of K_2PtCl_4 (0.207 g, 0.500 mmol) in DMSO (2.0 mL) was dropwise added. The mixture was stirred at 70.0 °C for 15 hours and then allowed to cool to room temperature. Methanol (10.0 mL) was added to precipitate the product. The precipitate was filtered, washed with methanol and dried at 50 °C in vacuum for 2 hours to give 0.15 g (41.7 %) of **(XI)**.

2.6.1.b Preparation of [4,4'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[1,3-benzenediolato-κO3]]platinum(II), (XII):

In the preparation of the title compound, the Schiff base ligand **(V)** was used in stead of **(IV)** and water was used to precipitate the complex **(XII)**. The yield was 0.10 g (36.5 %).

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2.6.1.c Preparation of [3,3'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[4-(hydroxy-κO)benzoato]]platinum(II), (XIII):

It was prepared as in section 2.6.1.b. The Schiff base ligand **(VI)** was used in stead of **(IV)** and water was used to precipitate the complex **(XIII)**. The yield was 0.15 g (49.7 %).

2.6.1.d Preparation of [2,2'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[5-(dimethylamino)phenolato-κO]]platinum(II), (XIV):

It was prepared as in section 2.6.1.b. The Schiff base ligand **(VII)** was used in stead of **(IV)** and water was used to precipitate the complex **(XIV)**. The yield was 0.15 g (49.9 %).

2.6.2 Preparation of Platinum Complexes with Schiff Bases Containing *trans*-DACH Ligand:

2.6.2.a Preparation of Sodium [3,3'-[*trans*-1,2-Cyclohexanediyl-bis[(nitrilo-κN)methylidyne]]bis[4-(hydroxy-κO)benzenesulfonato]]-platinate(II), (XV):

It was prepared as in section 2.6.1.a. The Schiff base ligand **(VIII)** was used in stead of **(IV)**. The yield was 0.12 g (33.3 %).

2.6.2.b Preparation of [4,4'-[*trans*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[1,3-benzenediolato-κO3]]platinum(II), (XVI):

It was prepared as in section 2.6.1.b. The Schiff base ligand **(IX)** was used in stead of **(V)**. The Yield was 0.10 g (36.5 %).

2.6.2.c [2,2'-[*cis*-1,2-Cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis-[5-(dimethylamino)phenolato-κO]]platinum(II), (XVII):

It was prepared as in section 2.6.1.d. The Schiff base ligand **(X)** was used in stead of **(VII)**. The yield was 0.12 g (39.9 %).

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3. RESULTS

Some physical properties for the starting materials, ligands and platinum complexes are shown in table 3.1.

Table 3.1: The color, molar masses, percent yields and melting points for the starting materials, Schiff base ligands and platinum complexes*.

Compound	Color	Molar Mass (g/mol)	Percent Yield (%)	Melting Point (°C)
***cis*-DACH.2HCl**	White	187.10	85.8	265.0 - 267.0
***trans*-DACH.2HCl**	White	187.10	94.1	245.0 - 247.0
I	Yellow	224.16	70.2	355.0 - 357.0 d.
II	Off-white	166.12	9.33	210.0 – 212.0
III	Off-white	165.19	55.9	74.0 -76.0
IV	Yellow	526.47	78.7	>360.0
V	Orange	354.39	85.4	260.0 - 262.0 d.
VI	Yellow	410.41	81.2	285.0 - 287.0 d.
VII	Yellow	408.52	50.2	190.0 - 192.0 d.
VIII	Yellow	526.47	74.6	>360.0
IX	Orange	354.39	86.2	250.0 - 252.0 d.
X	Yellow	408.52	62.2	167.0 - 169.0 d.
XI	Yellow	719.56	41.7	> 360.0
XII	Orange	547.48	36.5	300.0 - 302.0 d.
XIII	Yellow	603.50	49.7	310.0 - 312.0 d.
XIV	Yellow	601.61	49.9	280.0 - 282.0 d.
XV	Yellow	719.56	33.3	> 360.0
XVI	Orange	547.48	36.5	305.0 - 307.0 d.
XVII	Yellow	601.61	39.9	> 360.0

* d. : decomposition

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The results of solubility charts for the starting material, ligands and complexes are shown in table 3.2.

Table 3.2: The solubility* chart of the starting materials, Schiff base ligands and platinum complexes.**

Compound	Solvent										
	H_2O	MeOH	EtOH	Acetone	CH_2Cl_2	$CHCl_3$	Pet. Ether	Et_2O	n-C_6H_{14}	THF	DMSO
***cis*-DACH.2HCl**	+	+	–	–	–	–	–	–	–	–	+
***trans*-DACH.2HCl**	+	–	–	–	–	–	–	–	–	–	–
I	+	+	–	–	–	–	–	–	–	–	+
II	±	+	+	+	–	–	–	–	–	+	+
III	–	+	±	±	+	+	–	–	–	+	+
IV	+	±	–	–	–	–	–	–	–	–	+
V	–	–	–	–	–	–	–	–	–	–	+
VI	–	–	–	–	–	–	–	–	–	–	+
VII	–	–	±	+	+	+	–	–	–	+	+
VIII	+	±	–	–	–	–	–	–	–	–	+
IX	–	–	–	–	–	–	–	–	–	–	+
X	–	–	+	+	+	+	–	–	–	+	+
XI	+	–	–	–	–	–	–	–	–	–	+
XII	–	–	–	–	–	–	–	–	–	–	+
XIII	–	–	–	–	–	–	–	–	–	–	+
XIV	–	–	–	–	+	+	–	–	–	+	+
XV	+	–	–	–	–	–	–	–	–	–	+
XVI	–	–	–	–	–	–	–	–	–	–	+
XVII	–	–	–	–	–	±	–	–	–	–	+

*** 10 mg in 2 mL solvent.**

**** + : soluble, – : insoluble, ± :slightly soluble.**

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The results of Infrared (IR) for all prepared compounds are listed in table 3.3.

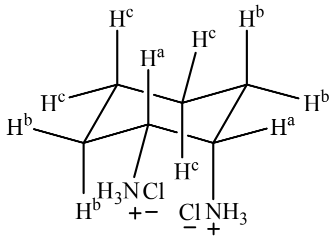
Table 3.3: The infrared stretching vibrations (cm^{-1}) for the starting materials, ligands and platinum complexes*.

COMPOUND	MODE					
	O-H	**C-H**	**C=O**	**C=C arm.**	**C=N**	**Others**
***cis*- DACH.2HCl**	_	2869 (m)	_	_	_	***υ* N-H** 3446 (s, br)
***trans*-DACH.2HCl**	_	2874 (m)	_	_	_	***υ* N-H** 3440 (s, br)
I	3432 (s, br)	3037 (m)	1661 (s)	1617 (m)	_	***υ* SO_3** 1192,1104 1037 (s)
II	3442 (s, br) 2590 (s, br)	2859 (m)	1668 (s)	1620 (m)	_	_
III	3457 (s, br)	2836 (m)	1646 (s)	1621 (s)	_	_
IV	3449 (s, br)	2937 (m)	_	1617 (w)	1632 (s)	***υ* SO_3** 1191,1109 1039 (s)
V	3437 (s, br)	2934 (m)	_	1524 (w)	1634 (s)	_
VI	3443 (s, br) 2700 (s, br)	2932 (m)	1666 (s)	1584 (w)	1633 (s)	_
VII	3421 (s, br)	2930 (m)	_	1582 (w)	1615 (s)	_
VIII	3449 (s, br)	2934 (m)	_	1582 (w)	1633 (s)	***υ* SO_3** 1180,1107 1034 (s)
IX	3423 (w, br)	2932 (m)	_	1597 (w)	1633 (s)	_
X	3422 (s, br)	2927 (m)	_	1564 (w)	1617 (s)	_
XI	_	2934 (m)	_	_	1603 (s)	***υ* SO_3** 1186,1116 1036 (s)
XII	3451 (m)	2931 (m)	_	_	1605 (s)	_
XIII	2584 (m, br)	2933 (m)	1688 (s)	_	1604 (s)	_
XIV	_	2927 (m)	_	_	1596 (s)	_
XV	_	2996 (m)	_	_	1603 (s)	***υ* SO_3** 1182,1114 1035 (s)
XVI	3404 (m)	2934 (m)	_	_	1607 (s)	_
XVII	_	2928 (m)	_	_	1594 (s)	_

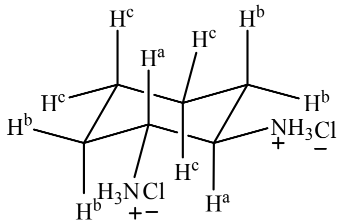
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The results of ^{1}H-NMR and ^{13}C-NMR for the starting materials are listed in tables 3.4- 3.9.

Table 3.4*: ^{1}H-NMR spectral data of *cis*-DACH.2HCl and *trans*-DACH.2HCl. #



cis-DACH.2HCl

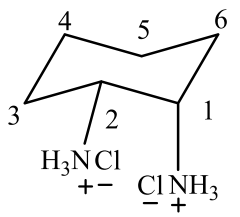


trans-DACH.2HCl

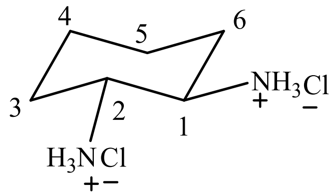
Compound	H- atom	H^a	H^b	H^c
***cis*-DACH.2HCl**	**δ (ppm)** ***J* value**	3.59 (t) *J* = 4.46 (2H)	1.69 (m) (4H)	1.38 (m) (4H)
***trans*-DACH.2HCl**	**Δ (ppm)**	3.22 (m) (2H)	2.00, 1.65 (m) (m) (2H) (2H)	1.35, 1.20 (m) (m) (2H) (2H)

***: in D_2O.**
#: (t) = triplet, (m) =multiplet.

Table 3.5*: ^{13}C-NMR spectral data of *cis*-DACH.2HCl and *trans*-DACH.2HCl.



cis-DACH.2HCl



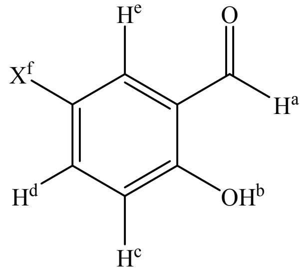
trans-DACH.2HCl

Compound	C-atom	C-1	C-2	C-3	C-4	C-5	C-6
***cis*-DACH.2HCl**	**δ (ppm)**	49.9	52.2	25.7	29.2	20.2	22.7
***trans*-DACH.2HCl**	**δ (ppm)**	52.2	52.2	29.2	29.2	22.7	22.7

***: in D_2O.**

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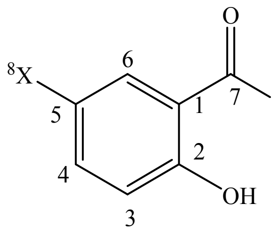
Table 3.6*: [1]H-NMR spectral data of I and II [#].



Compound	X	H- atom	H^a	H^b	H^c	H^d	H^e	H^f
I	SO_3Na	**δ (ppm)** ***J* value (Hz)**	10.23 (s) (1H)	10.88 (s) broad (1H)	6.90 (d) $^3J = 8.5$ (1H)	7.68 (dd) $^3J = 8.5$ $^4J = 2.3$ (1H)	7.86 (d) $^4J = 2.3$ (1H)	_
II	$COOH^f$	**δ (ppm)** ***J* value (Hz)**	10.26 (s) (1H)	11.69 (s) broad (1H)	7.04 (d) $^3J = 8.7$ (1H)	8.00 (dd) $^3J = 8.7$ $^4J = 2.2$ (1H)	8.20 (d) $^3J = 2.2$ (1H)	12.64 (s) broad (1H)

***: in DMSO-d_6**
#: (s) = singlet, (d) = doublet, (dd) = doublet of doublet.

Table 3.7*: [13]C-NMR spectral data of I and II.

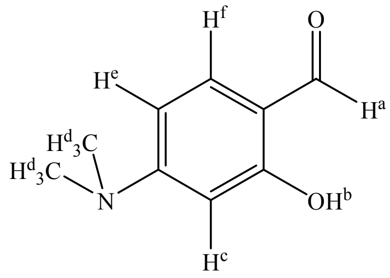


Compound	X	C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
I	**SO_3Na**	**δ (ppm)**	121.5	161.3	117.1	134.2	140.4	126.6	191.8	_
II	**COOH**	**δ (ppm)**	122.5	164.6	118.0	137.3	122.4	131.2	191.1	166.9

***: in DMSO-d_6**

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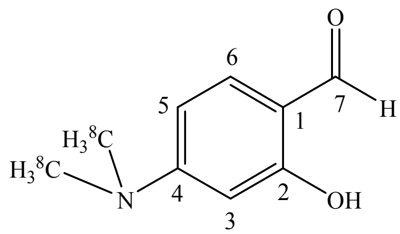
Table 3.8*: ¹H-NMR spectral data of III.



H-atom	H^a	H^b	H^c	H^d	H^e	H^f
δ (ppm) *J* value (Hz)	9.50 (s) (1H)	11.58 (s) (1H)	6.06 (d) $^4J = 2.3$ (1H)	3.04 (s) (6 H)	6.26 (dd) $^3J = 8.9$ $^4J = 2.3$ (1H)	7.26 (d) $^3J = 8.9$ (1H)

***: in $CDCl_3$.**

Table 3.9*: ¹³C-NMR spectral data of III.



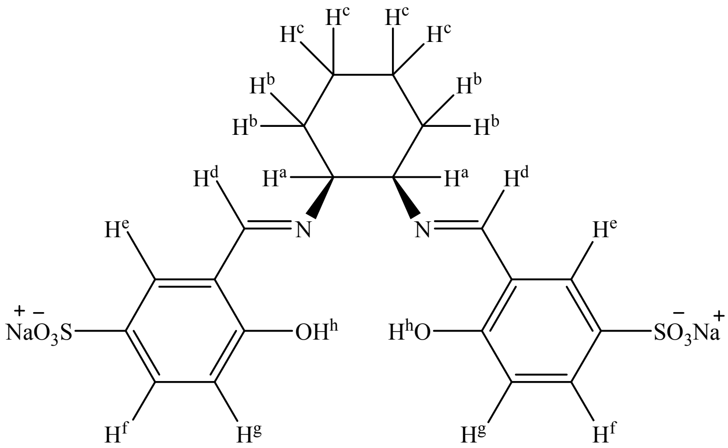
C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
δ (ppm)	111.7	164.3	97.3	156.2	104.6	135.2	192.4	40.1

***: in $CDCl_3$.**

The results of ^{1}H-NMR and ^{13}C-NMR for the Schiff base ligands and their platinum complexes are listed in tables 3.10- 3.38.

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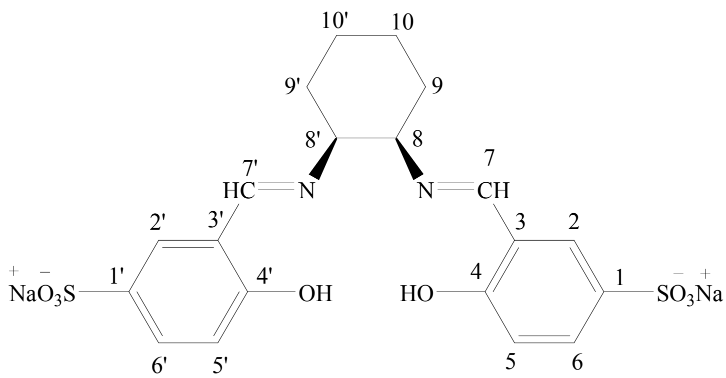
Table 3.10*: [1]H-NMR spectral data of IV.



H-atom	H^a	H^b + H^c	H^d	H^e	H^f	H^g	H^h
δ (ppm) *J* value (Hz)	3.67 (m) (2H)	1.74 + 1.71 (m) (m) (6H) + (2H)	8.60 (s) (2H)	7.65 (d) $^{4}J = 2.1$ (2H)	7.50 (dd) $^{3}J = 8.6$ $^{4}J = 2.1$ (2H)	6.75 (d) $^{3}J = 8.6$ (2H)	13.90 (s) (2H)

***: in DMSO-d_6**

Table 3.11*: [13]C-NMR spectral data of IV.

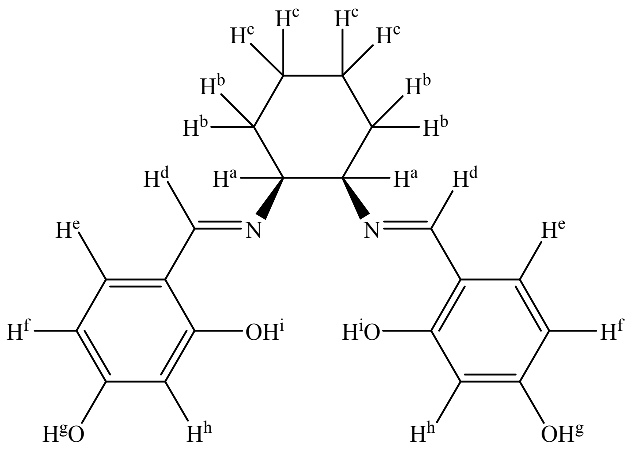


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	139.3	130.4	117.6	161.8	116.4	129.5	165.8	68.2	30.9	22.4

***: in DMSO-d_6**

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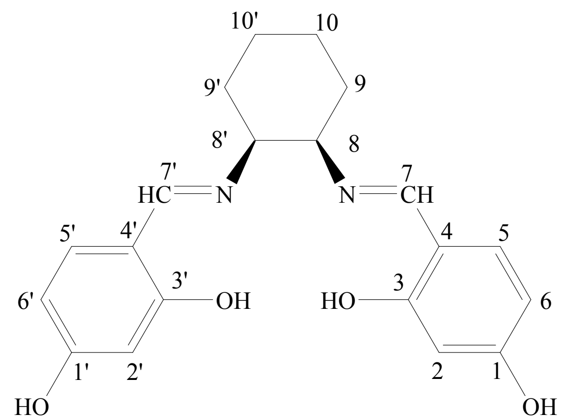
Table 3.12*: [1]H-NMR spectral data of V.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h	H^i
δ (ppm) *J* value (Hz)	3.54 (m) (2H)	1.69 (m) + 1.48 (m) (6H) + (2H)	8.32 (s) (2H)	7.13 (d) $^3J = 8.5$ (2H)	6.22 (dd) $^3J = 8.5$ $^4J = 2.3$ (2H)	9.87 (s) (2H)	6.09 (d) $^4J = 2.3$ (2H)	13.97 (s) (2H)

***: in DMSO-d_6**

Table 3.13*: [13]C-NMR spectral data of V.

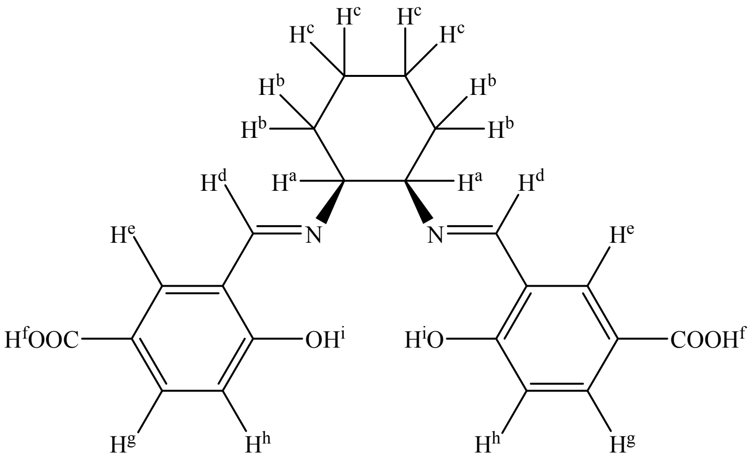


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	162.2	103.0	165.2	111.9	133.9	107.3	164.4	67.5	30.9	22.4

***: in DMSO-d_6**

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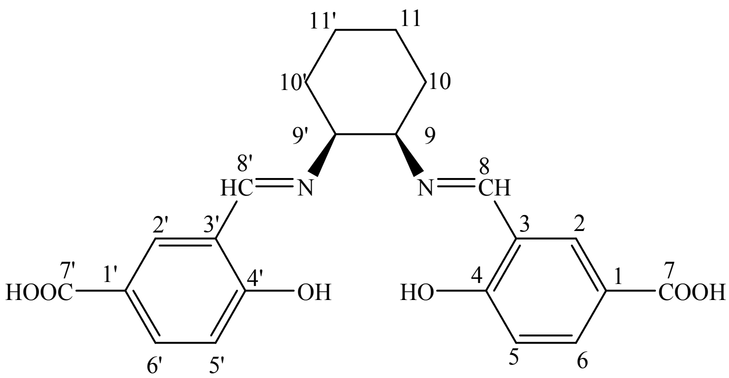
Table 3.14*: ^{1}H-NMR spectral data of VI.



H-atom	H^a	H^b + H^c	H^d	H^e	H^f	H^g	H^h	H^i
δ (ppm) *J* value (Hz)	3.75 (m) (2H)	1.87 + 1.55 (m) (m) (6H) + (2H)	8.68 (s) (2H)	8.02 (s) (2H)	_	7.81 (d) ^3J = 8.8 (2 H)	6.82 (d) ^3J = 8.8 (2H)	14.50 (s) (2H)

***: in DMSO-d$_6$**

Table 3.15*: ^{13}C-NMR spectral data of VI.

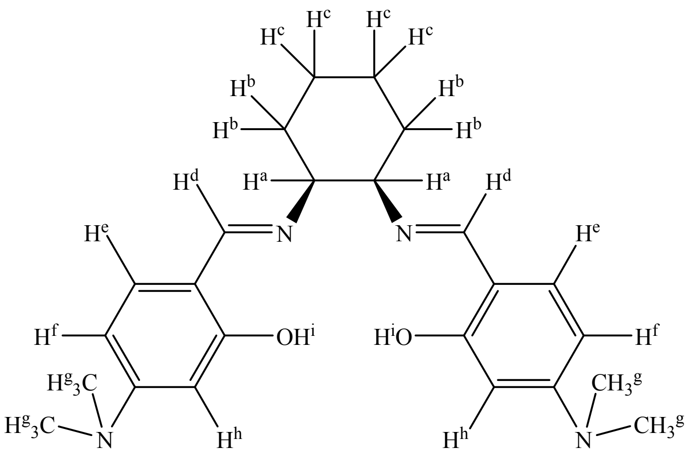


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
δ (ppm)	134.7	-	-	166.1	118.0	-	167.3	166.8	67.2	-	22.4

***: in DMSO-d$_6$**

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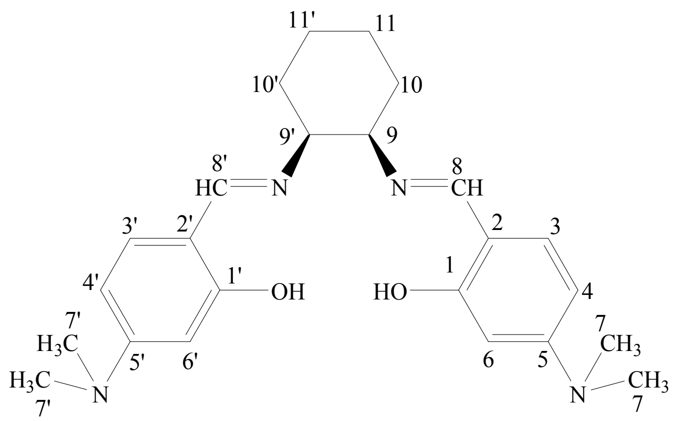
Table 3.16*: [1]H-NMR spectral data of VII.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h	H^i
δ (ppm) *J* value (Hz)	3.49 (m) (2H)	1.82 + 1.52 (m) (m) (6H) (2H)	8.02 (s) (2H)	6.97 (d) $^3J = 8.7$ (2H)	6.14 (dd) $^3J = 8.7$ $^4J = 2.4$ (2H)	2.96 (s) (12 H)	6.07 (d) $^4J = 2.4$ (2H)	13.98 (s) (2H)

***: in $CDCl_3$**

Table 3.17*: [13]C-NMR spectral data of VII.

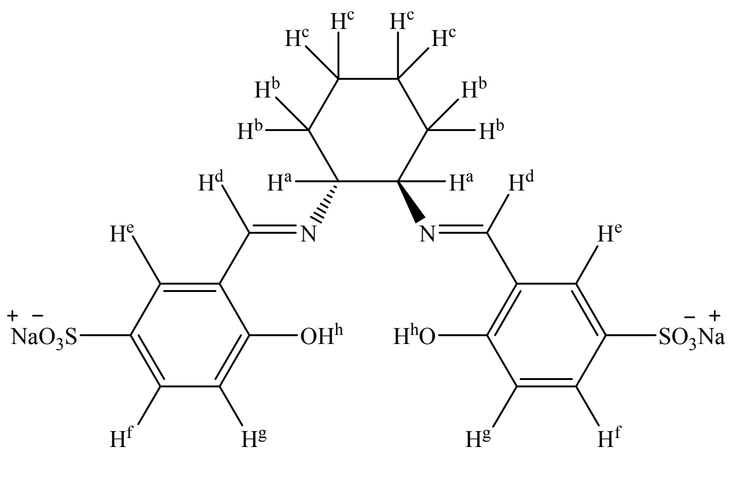


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
δ (ppm)	166.1	109.1	132.8	103.4	153.9	99.2	40.1	162.4	67.3	30.4	22.6

***: in $CDCl_3$**

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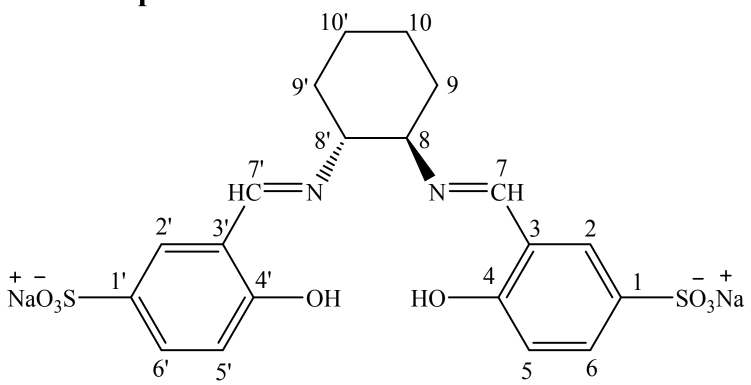
Table 3.18*: ^{1}H-NMR spectral data of VIII.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h
δ (ppm) *J* value (Hz)	–	1.80 +1.56 (m) (m) (4H) + (4H)	8.53 (s) (2H)	7.61 (d) $^{4}J = 2.1$ (2H)	7.47 (dd) $^{3}J = 8.6$ $^{4}J = 2.1$ (2H)	6.72 (d) $^{3}J = 8.6$ (2H)	13.51 (s) (2H)

***: in DMSO-d_6**

Table 3.19*: ^{13}C-NMR spectral data of VIII.

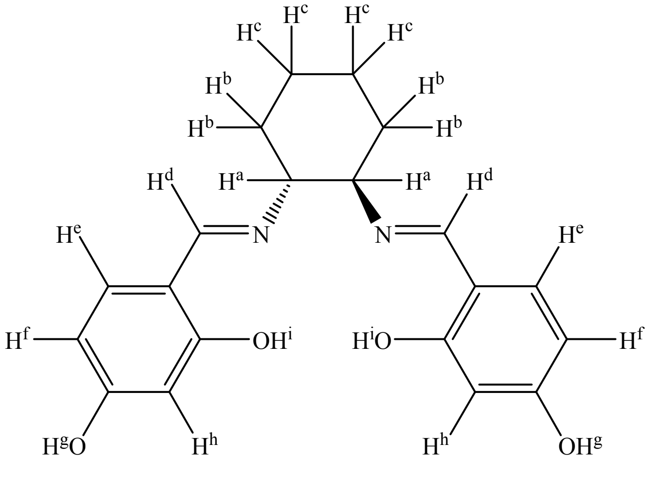


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	139.1	130.3	117.6	161.5	116.3	129.3	165.5	71.3	32.9	24.2

***: in DMSO-d_6**

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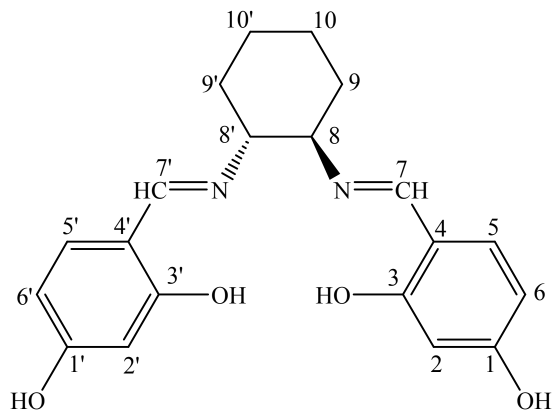
Table 3.20*: ^{1}H-NMR spectral data of IX.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h	H^i
δ (ppm) *J* value (Hz)	3.33 (m) (2H)	1.77 + 1.42 (m) (m) (4H) (4H)	8.23 (s) (2H)	7.05 (d) $^{3}J = 8.4$ (2H)	6.18 (d d) $^{3}J = 8.4$ $^{4}J = 2.2$ (2H)	9.55 (s) (2H)	6.08 (d) $^{4}J = 2.2$ (2H)	13.62 (s) (2H)

***: in DMSO-d_6**

Table 3.21*: ^{13}C-NMR spectral data of IX.

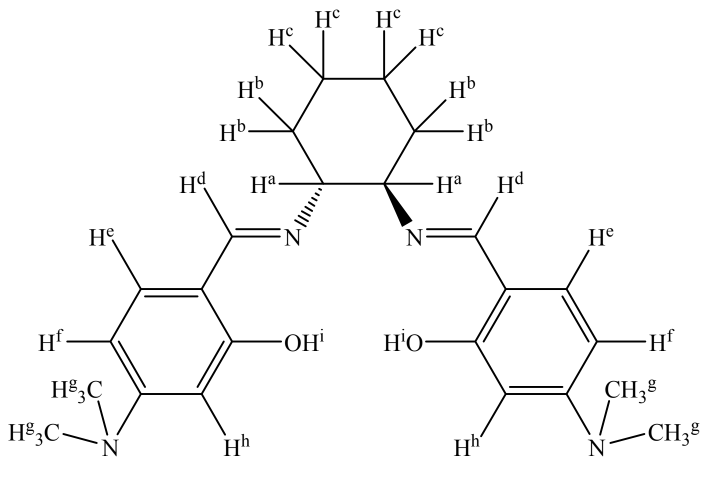


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	162.0	102.9	164.6	111.6	133.7	107.4	164.3	71.0	33.2	24.3

***: in DMSO-d_6**

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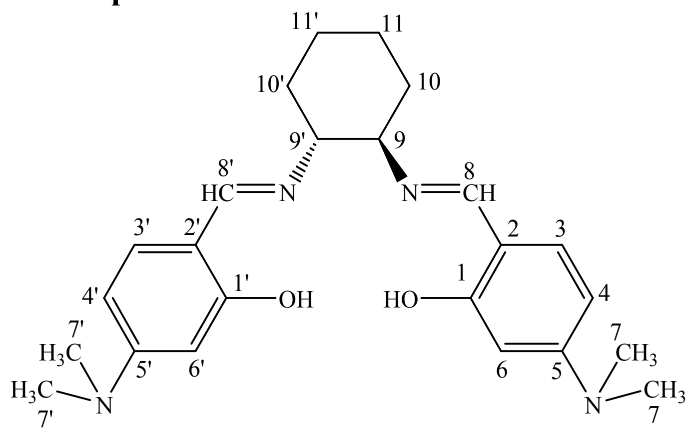
Table 3.22*: ^{1}H-NMR spectral data of X.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h	H^i
δ (ppm) *J* value (Hz)	3.15 (m) (2H)	1.94 +1.82 +1.63+1.41 (m) (m) (m) (m) (2H) (2H) (2H) (2H)	7.99 (s) (2H)	6.89 (d) ^{3}J=8.5 (2H)	6.14 (d) ^{3}J =2.4 (2H)	2.94 (s) (12 H)	6.07 (s) (2H)	13.66 (s) (2H)

***: in $CDCl_3$**

Table 3.23*: ^{13}C-NMR spectral data of X.

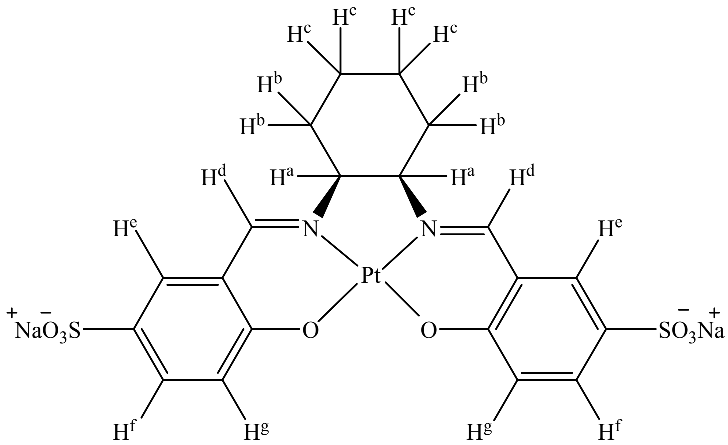


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
δ (ppm)	165.4	108.7	132.9	103.5	153.9	98.9	40.1	163.1	70.9	33.2	24.4

***: in $CDCl_3$**

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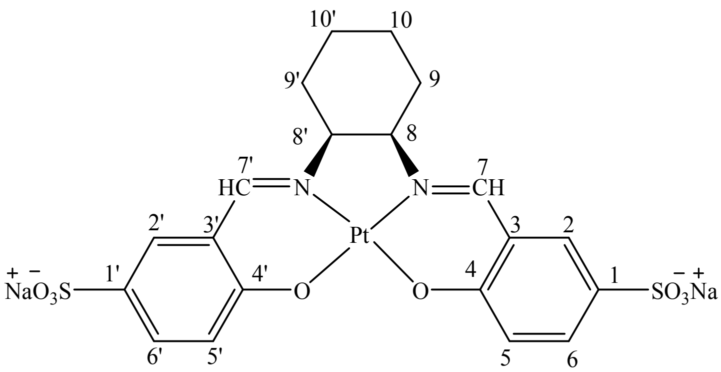
Table 3.24*: ^{1}H-NMR spectral data of XI.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g
δ (ppm) *J* value (Hz)	3.96 (m) (2H)	2.23 +1.80 + 1.39 (m) (m) (m) (2H) (2H) (4H)	8.52 (s) (2H)	7.84 (d) ^{4}J =1.8 (2H)	7.59 (d d) ^{3}J = 8.8 ^{4}J = 1.8 (2H)	6.80 (d) ^{3}J = 8.8 (2H)

***: in DMSO-d_6**

Table 3.25*: ^{13}C-NMR spectral data of XI.

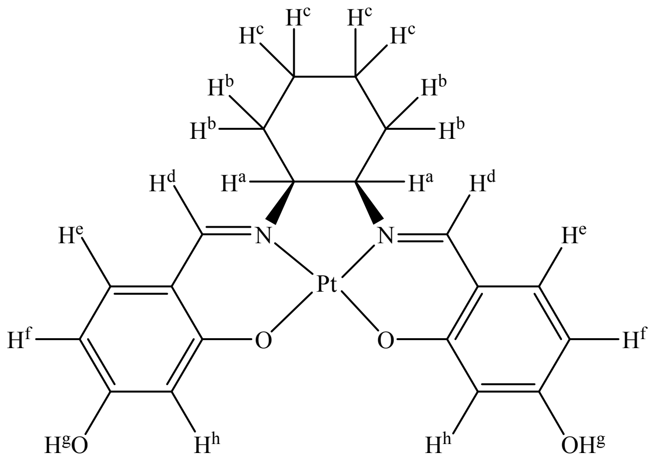


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	136.7	131.8	121.2	162.8	120.4	131.8	155.3	70.8	27.4	21.4

***: in DMSO-d_6**

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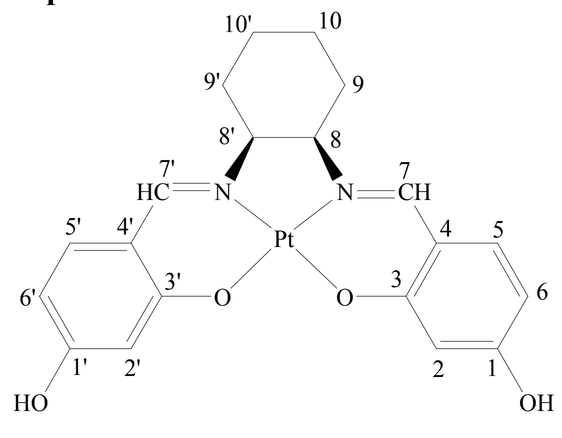
Table 3.26*: [1]H-NMR spectral data of XII.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h
δ (ppm) *J* value (Hz)	3.80 (m) (2H)	2.16 + 1.76 + 1.36 (m) (m) (m) (2H) (2H) (4H)	8.14 (s) (2H)	7.30 (d) $^3J = 8.0$ (2H)	6.10 (d) $^3J = 8.0$ (2H)	9.82 (s) (2H)	6.22 (s) (2H)

***: in DMSO-d_6**

Table 3.27*: [13]C-NMR spectral data of XII.

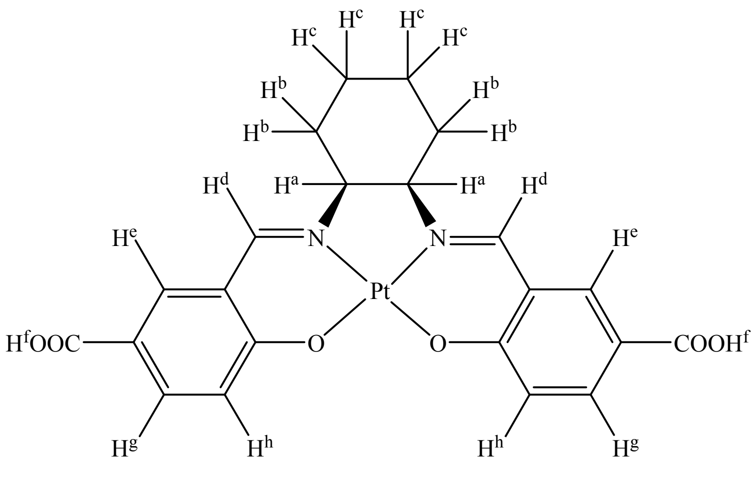


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	163.2	105.0	164.9	116.6	136.0	107.0	153.5	70.3	27.3	21.5

***: in DMSO-d_6**

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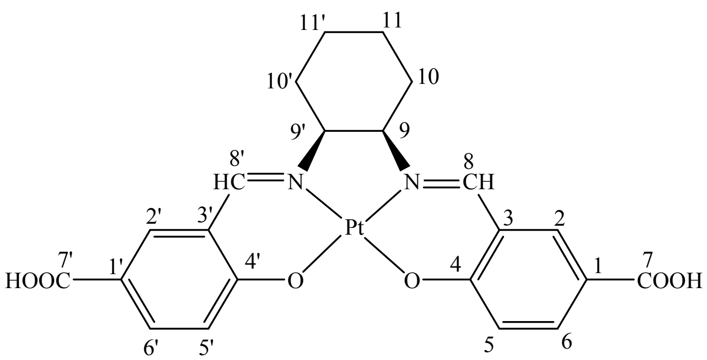
Table 3.28*: [1]H-NMR spectral data of XIII.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h
δ (ppm)	4.00 (m) (2H)	1.82 + 1.39 (m) (m) (3H) (5H)	8.60 (s) (2H)	8.30 (s) (br) (2 H)	12.41 (s) (br) (2 H)	7.91 (s) (br) (2H)	6.90 (s) (br) (2H)

***: in DMSO-d_6**

Table 3.29*: [13]C-NMR spectral data of XIII.

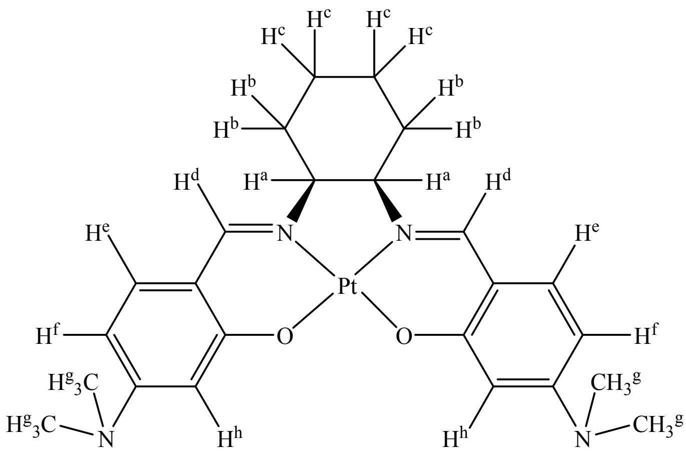


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
δ (ppm)	138.2	134.3	122.7	165.9	118.6	138.2	167.2	156.0	71.1	27.3	21.4

***: in DMSO-d_6**

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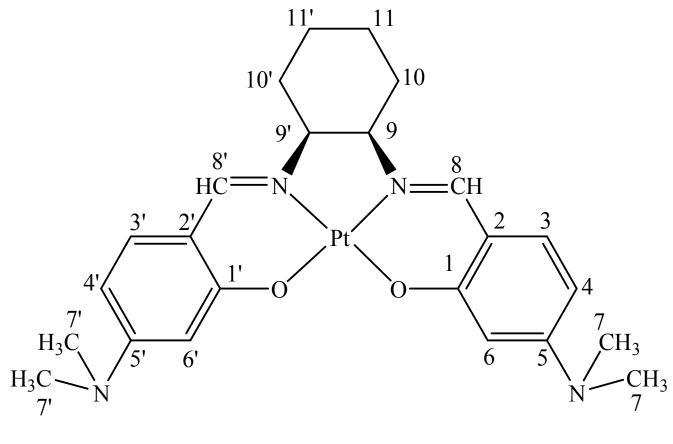
Table 3.30*: [1]H-NMR spectral data of XIV.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h
δ (ppm) *J* value (Hz)	3.72 (m) (2H)	2.24 + 1.52 (m) (m) (4H) (4H)	7.69 (s) (2H)	7.09 (d) $^3J = 9.0$ (2H)	6.11 (d) $^3J = 9.0$ (2H)	2.59 (s) (12 H)	6.46 (s) (2H)

***: in $CDCl_3$**

Table 3.31*: [13]C-NMR spectral data of XIV.

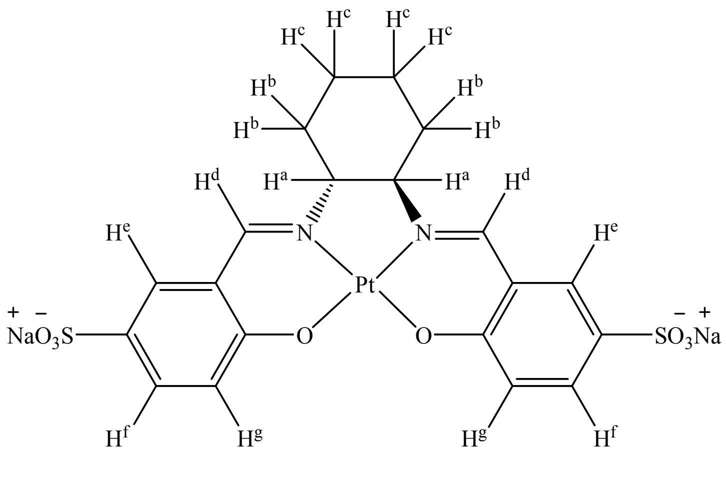


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
δ (ppm)	164.9	109.1	134.4	103.6	154.7	102.4	40.2	150.9	70.4	27.4	21.5

***: in $CDCl_3$**

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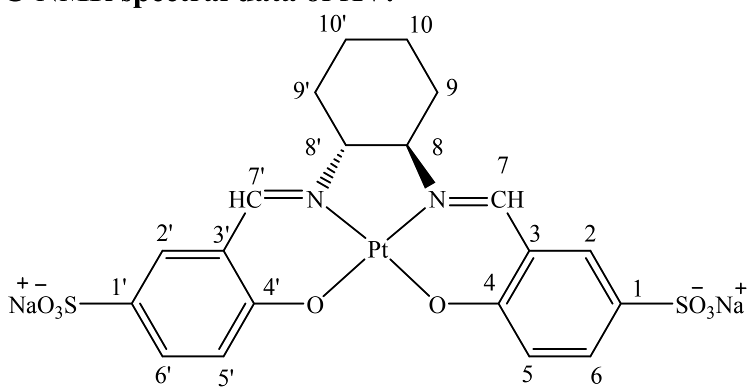
Table 3.32*: ^{1}H-NMR spectral data of XV.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g
δ (ppm) *J* value (Hz)	3.51 (m) (2H)	1.73 +1.30 (m) (m) (3H) (5H)	8.45 (s) (2H)	7.91 (d) $^{4}J = 1.7$ (2H)	7.58 (dd) $^{3}J = 8.8$ $^{4}J = 1.7$ (2H)	6.79 (d) $^{3}J = 8.8$ (2H)

***: in DMSO-d$_6$**

Table 3.33*: ^{13}C-NMR spectral data of XV.

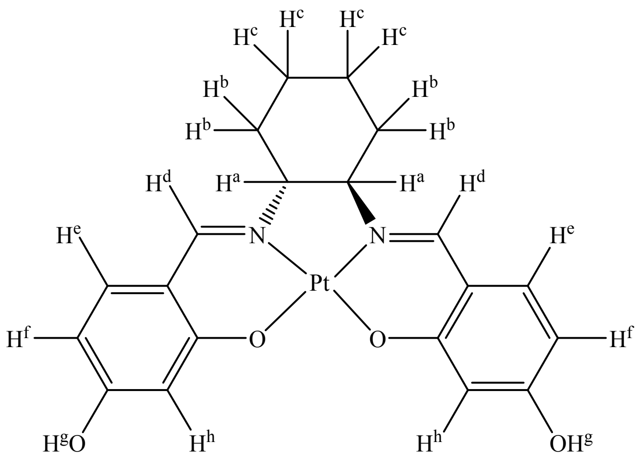


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	136.6	132.2	121.0	163.1	120.4	131.9	153.1	74.2	27.9	24.7

***: in DMSO-d$_6$**

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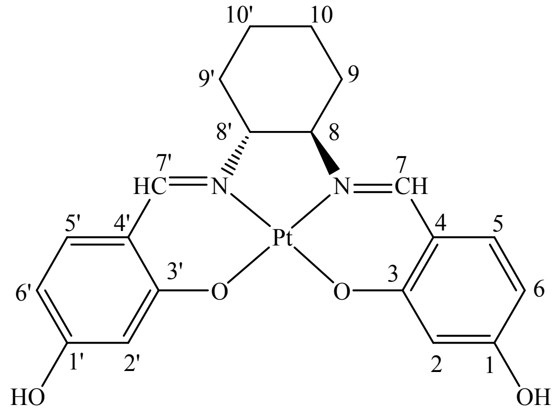
Table 3.34*: [1]H-NMR spectral data of XVI.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^h	H^g	H^f
δ (ppm) ***J* value (Hz)**	2.62 (m) (2H)	1.73 + 1.36 (m) (m) (3H) + (5H)	8.07 (s) (2H)	7.33 (d) $^3J = 8.0$ (2H)	6.20 (s) (2H)	9.84 (s) (2H)	6.09 (d) $^3J = 8.0$ (2H)

***: in DMSO-d$_6$**

Table 3.35*: [13]C-NMR spectral data of XVI.

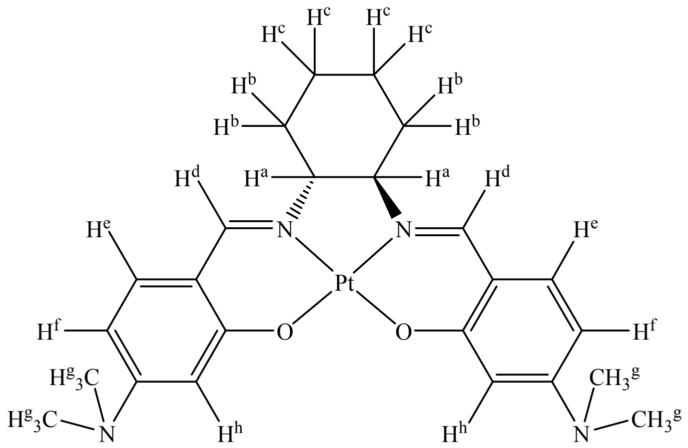


C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
δ (ppm)	163.2	105.0	165.2	116.4	136.4	106.9	151.3	73.7	28.0	24.3

***: in DMSO-d$_6$**

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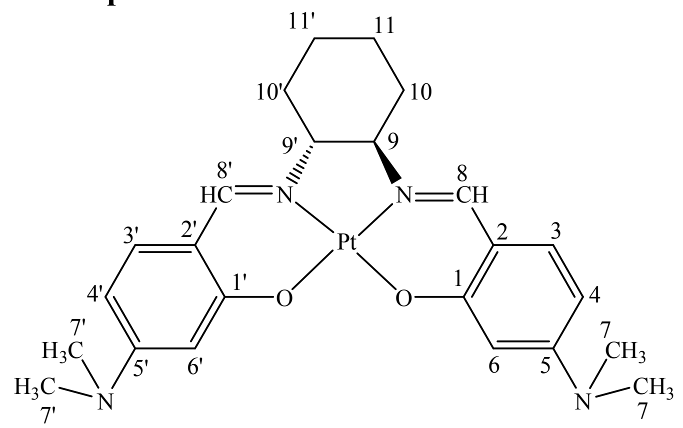
Table 3.36*: ^{1}H-NMR spectral data of VII.



H-atom	H^a	$H^b + H^c$	H^d	H^e	H^f	H^g	H^h
δ (ppm) *J* value (Hz)	3.18 (m) (2H)	1.90+1.84+1.53+1.41 (m) (m) (m) (m) (2H) (2H) (2H) (2H)	7.95 (s) (2H)	6.89 (d) $^{3}J = 8.7$ (2H)	6.08 (dd) $^{3}J = 8.7$ $^{4}J = 2.3$ (2H)	2.96 (s) (12 H)	6.04 (d) $^{4}J = 2.3$ (2H)

***: in $CDCl_3$**

Table 3.37*: ^{13}C-NMR spectral data of VII.



C-atom	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
δ (ppm)	-	99.9	128.1	98.6	130.5	94.2	35.4	158.4	66.2	28.5	-

***: in $CDCl_3$**

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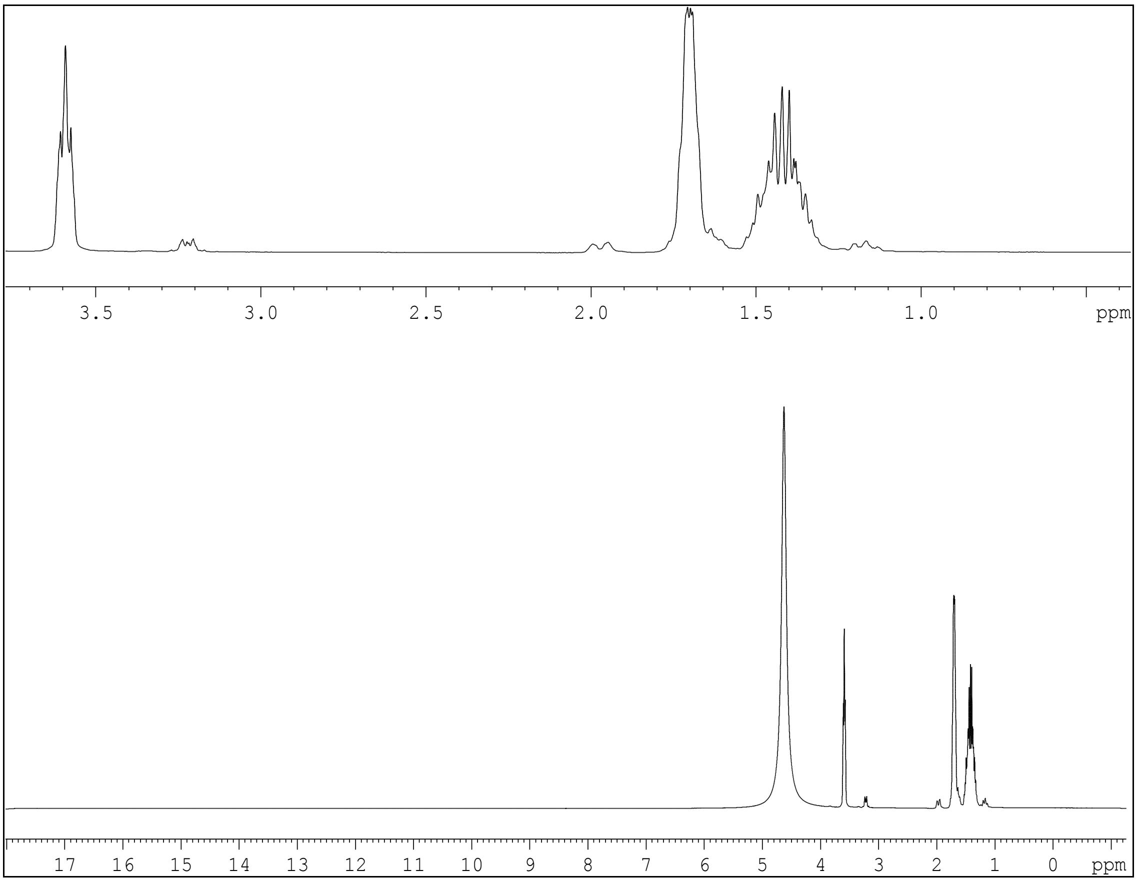


Figure 3.1: ^{1}H-NMR Spectrum of *cis*-DACH.2HCl

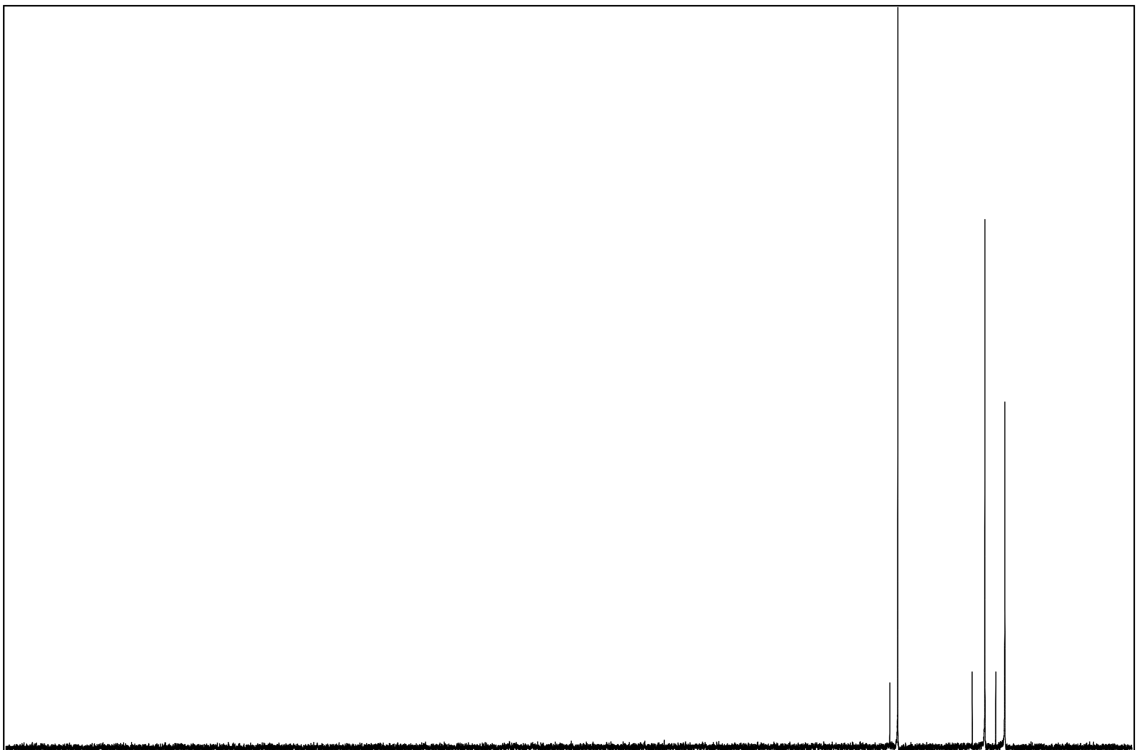


Figure 3.2: ^{13}C-NMR Spectrum of *cis*-DACH.2HCl

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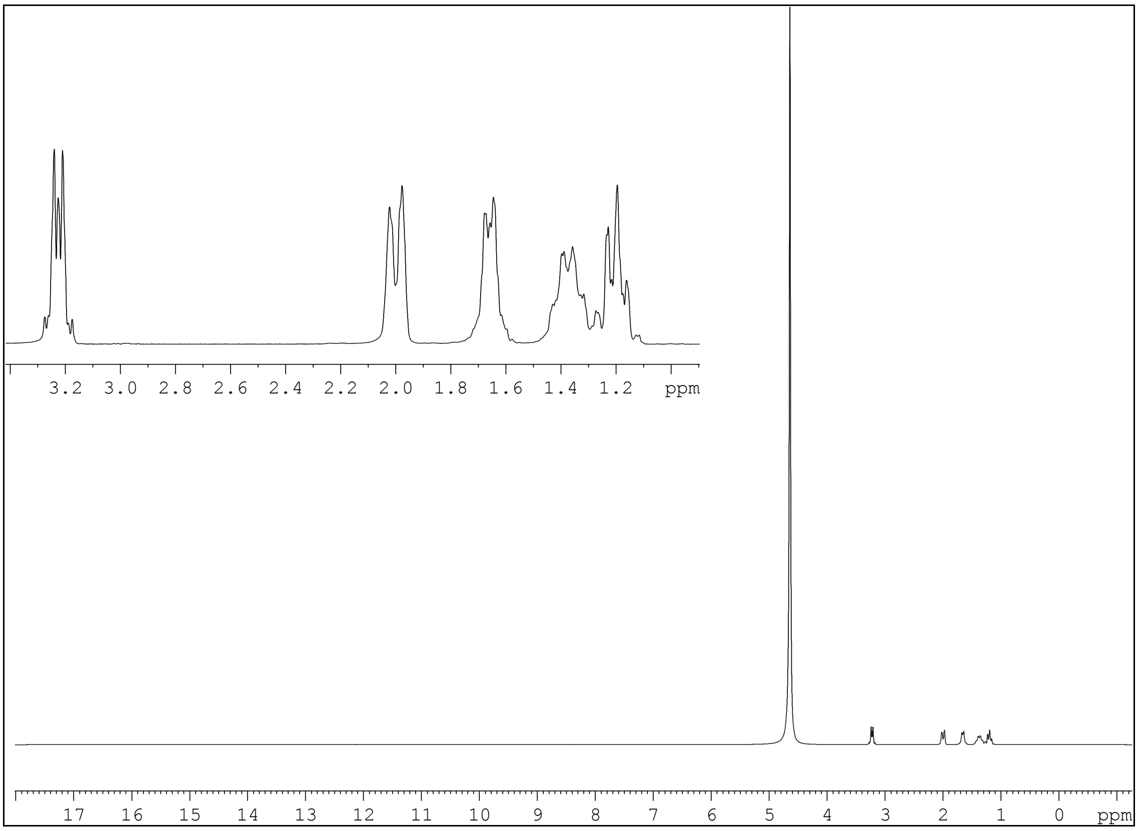


Figure 3.3: ^{1}H-NMR Spectrum of *trans*-DACH.2HCl

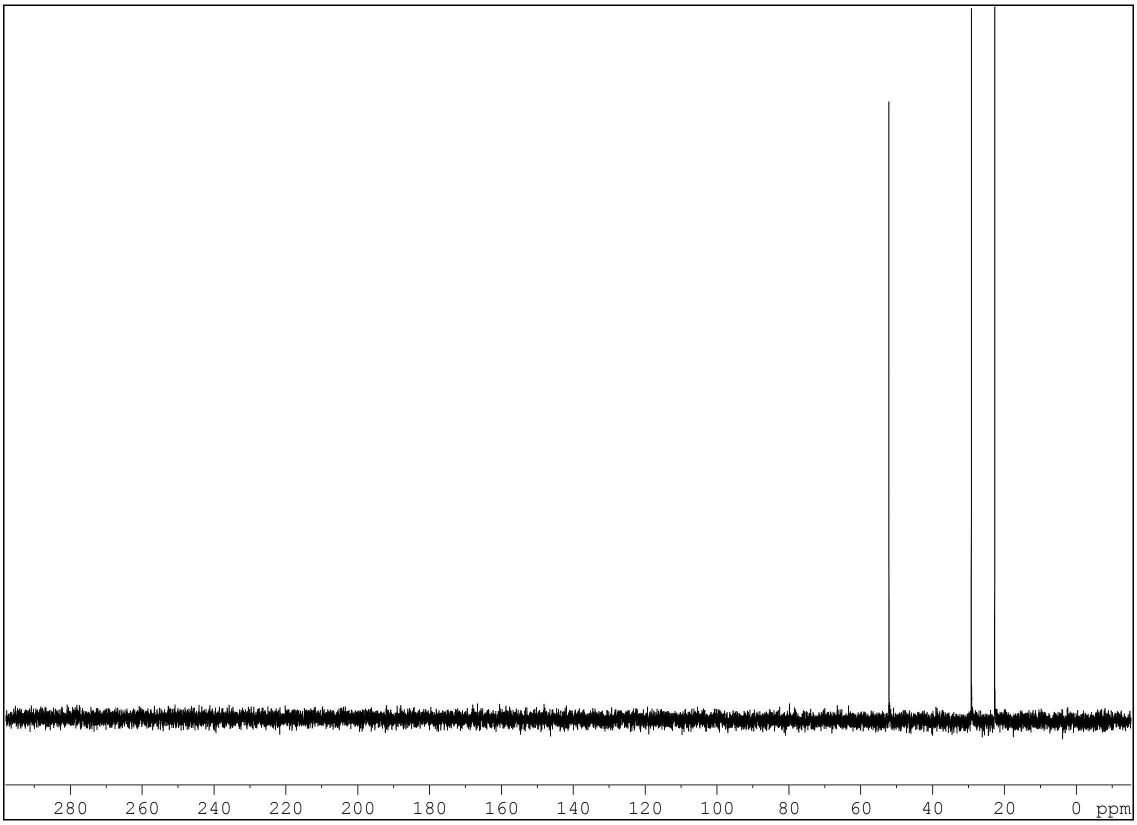


Figure 3.4: ^{13}C-NMR Spectrum of *trans*-DACH.2HCl

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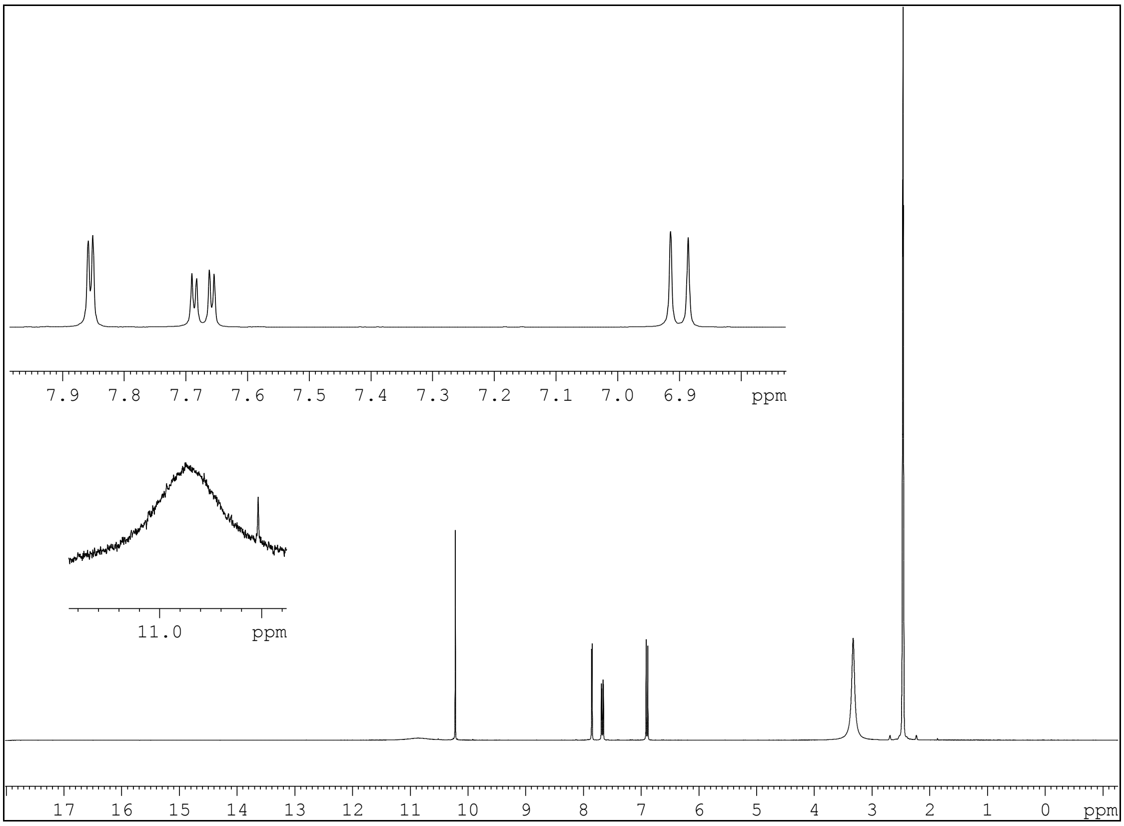


Figure 3.5: ^{1}H-NMR Spectrum of **(I)**.

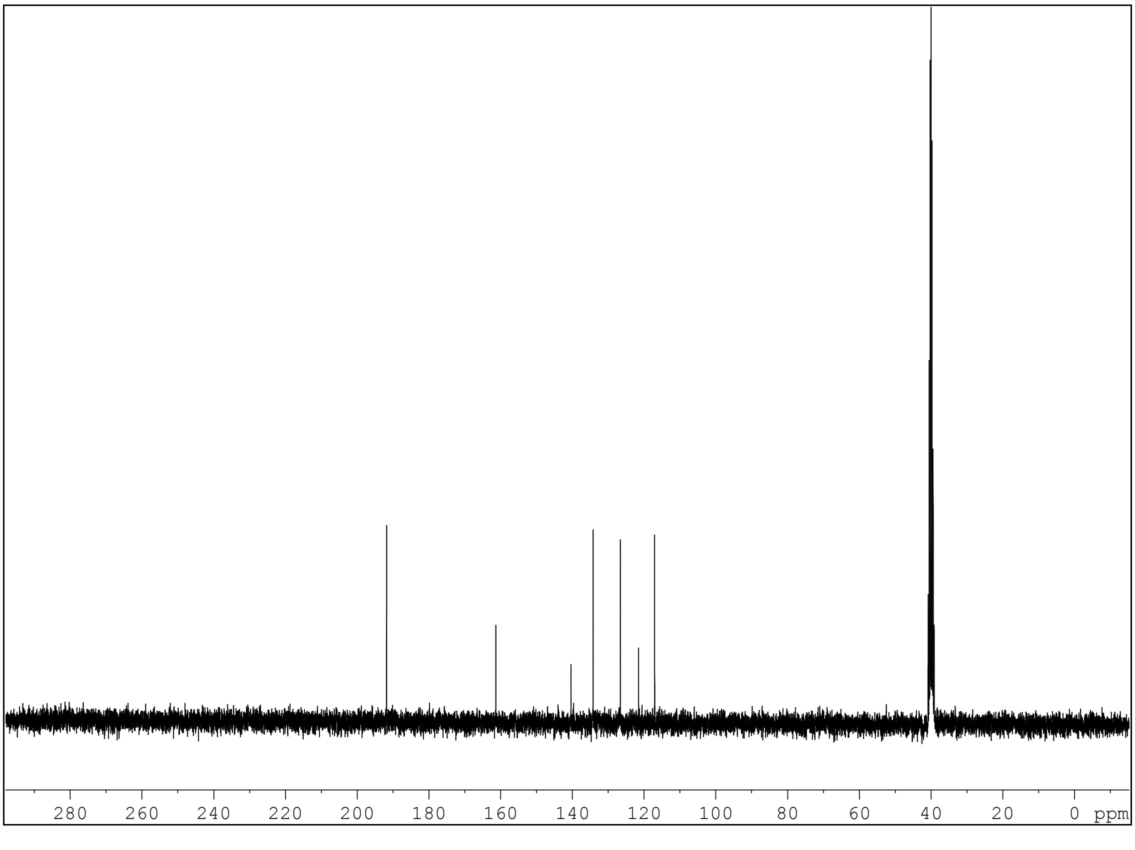


Figure 3.6: ^{13}C-NMR Spectrum of **(I)**.

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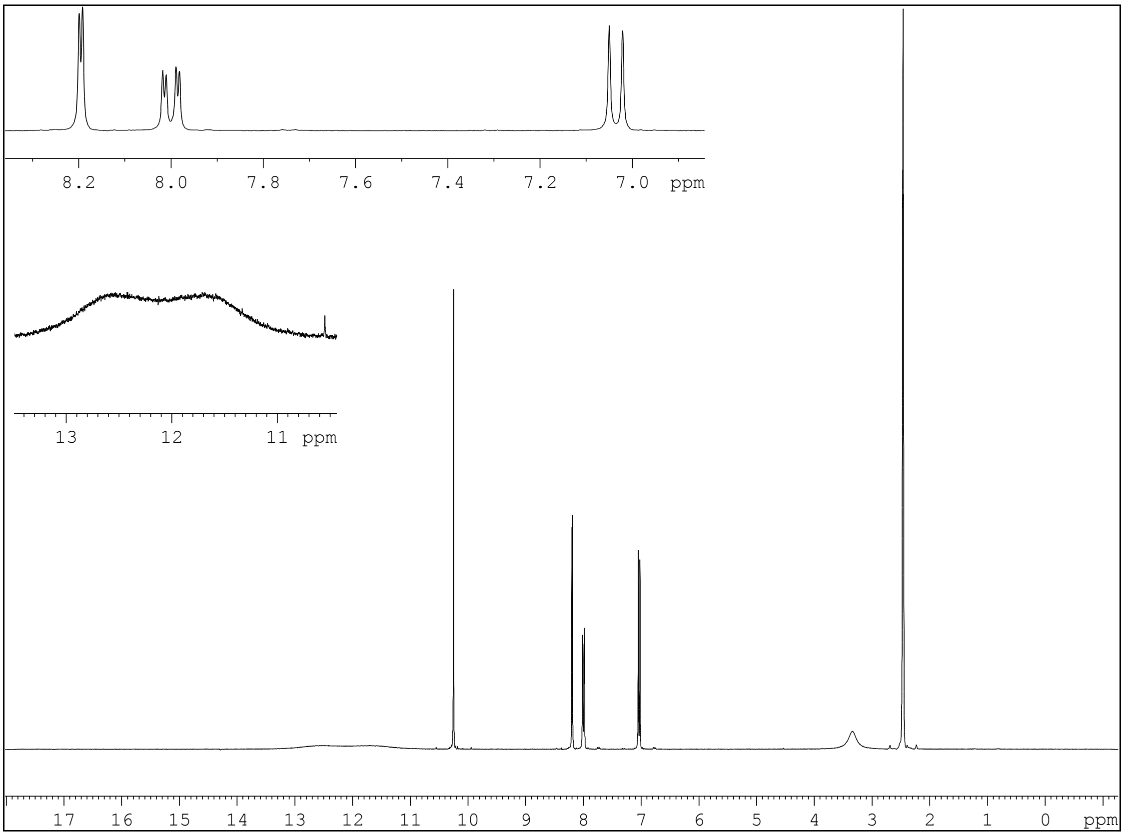


Figure 3.7: ^{1}H-NMR Spectrum of **(II)**.

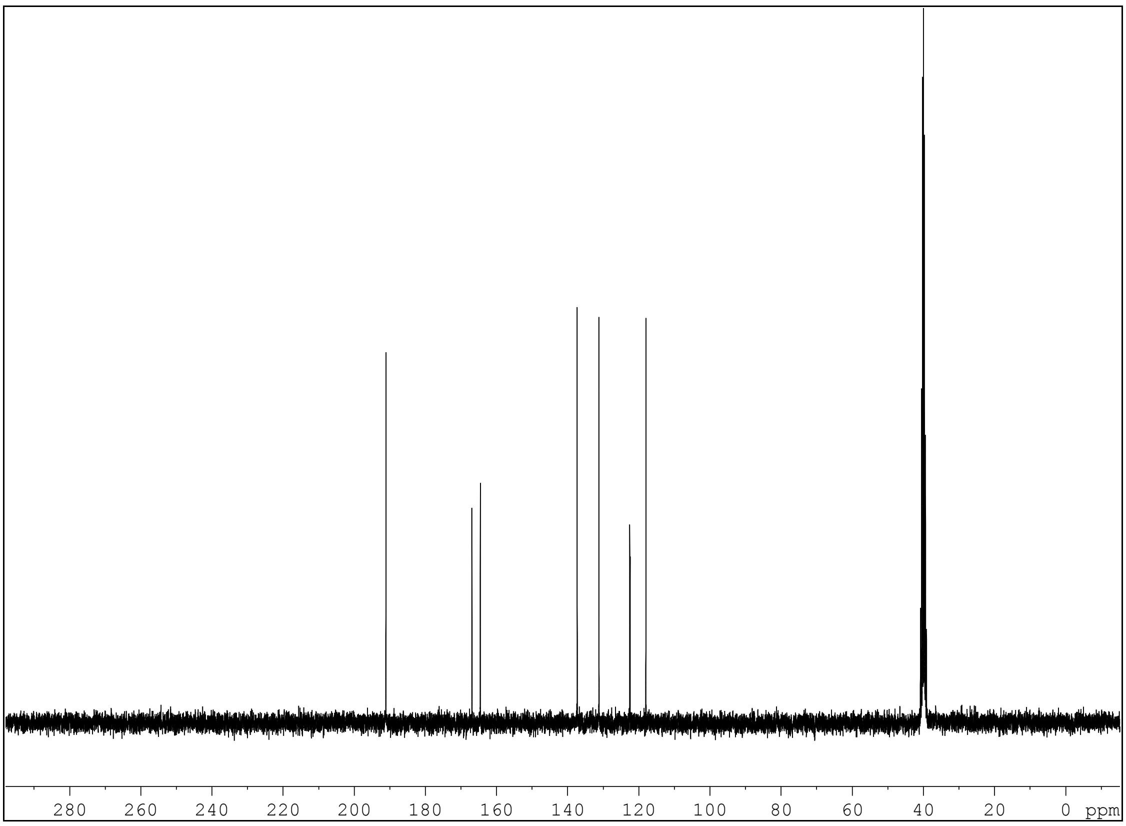


Figure 3.8: ^{13}C-NMR Spectrum of **(II)**.

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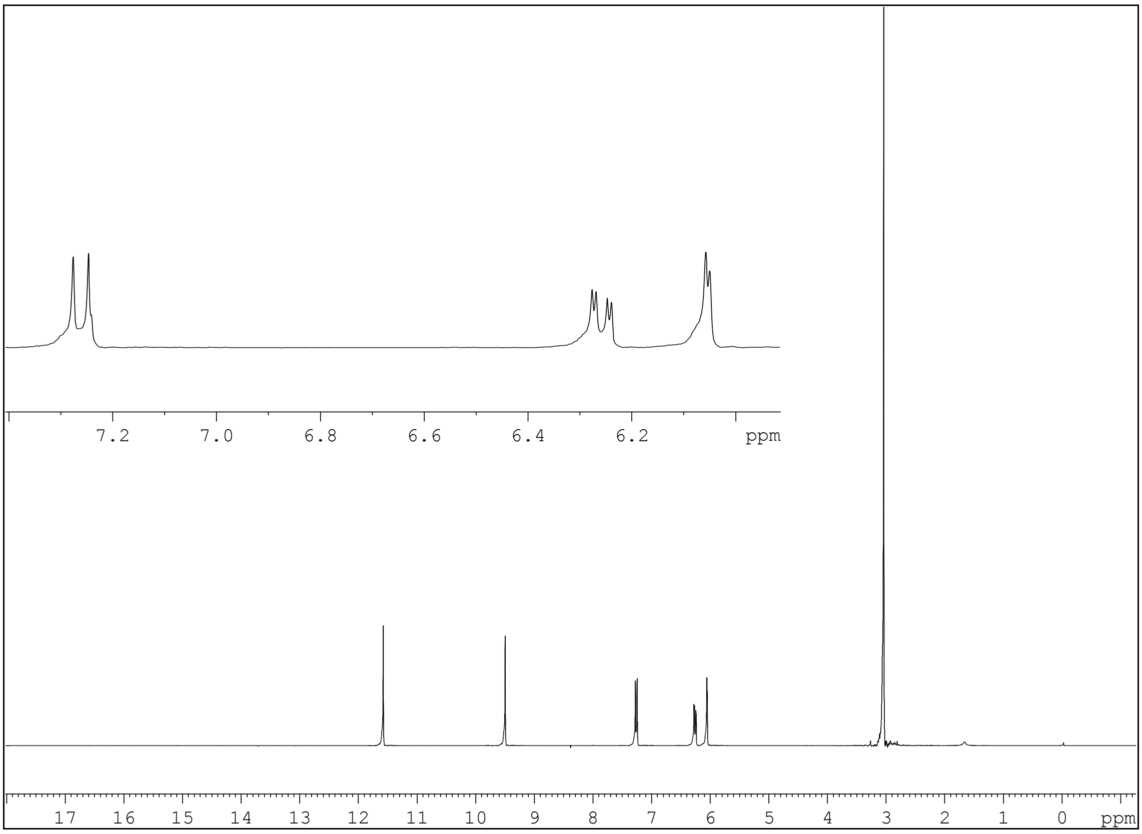


Figure 3.9: ^{1}H-NMR Spectrum of **(III)**.

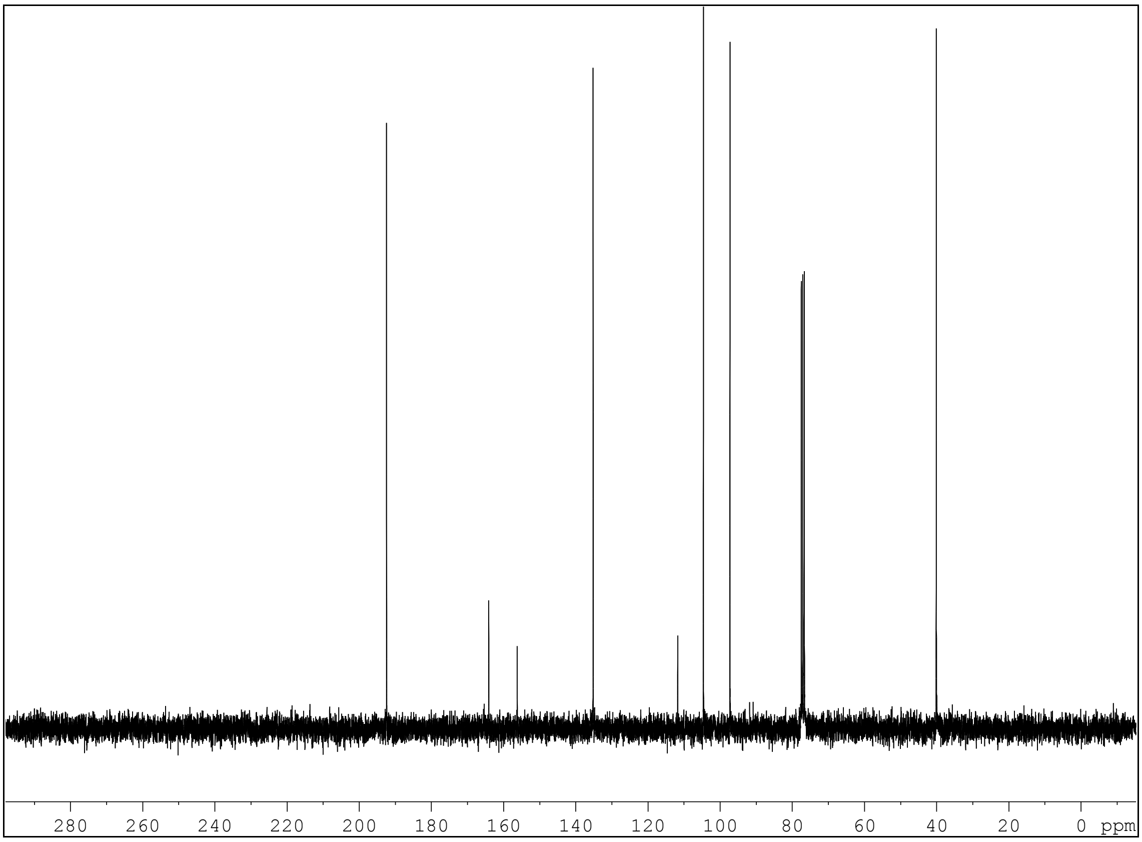


Figure 3.10: ^{13}C-NMR Spectrum of **(III)**.

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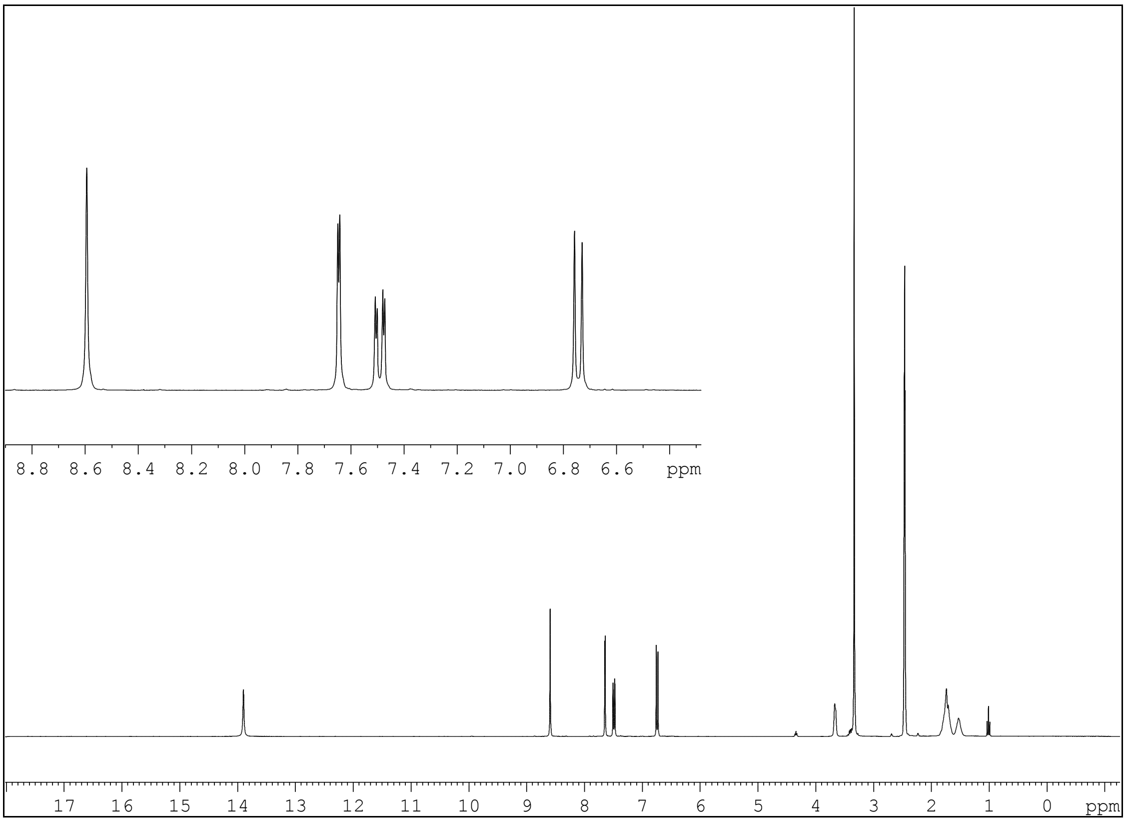


Figure 3.11: ^{1}H-NMR Spectrum of **(IV)**.

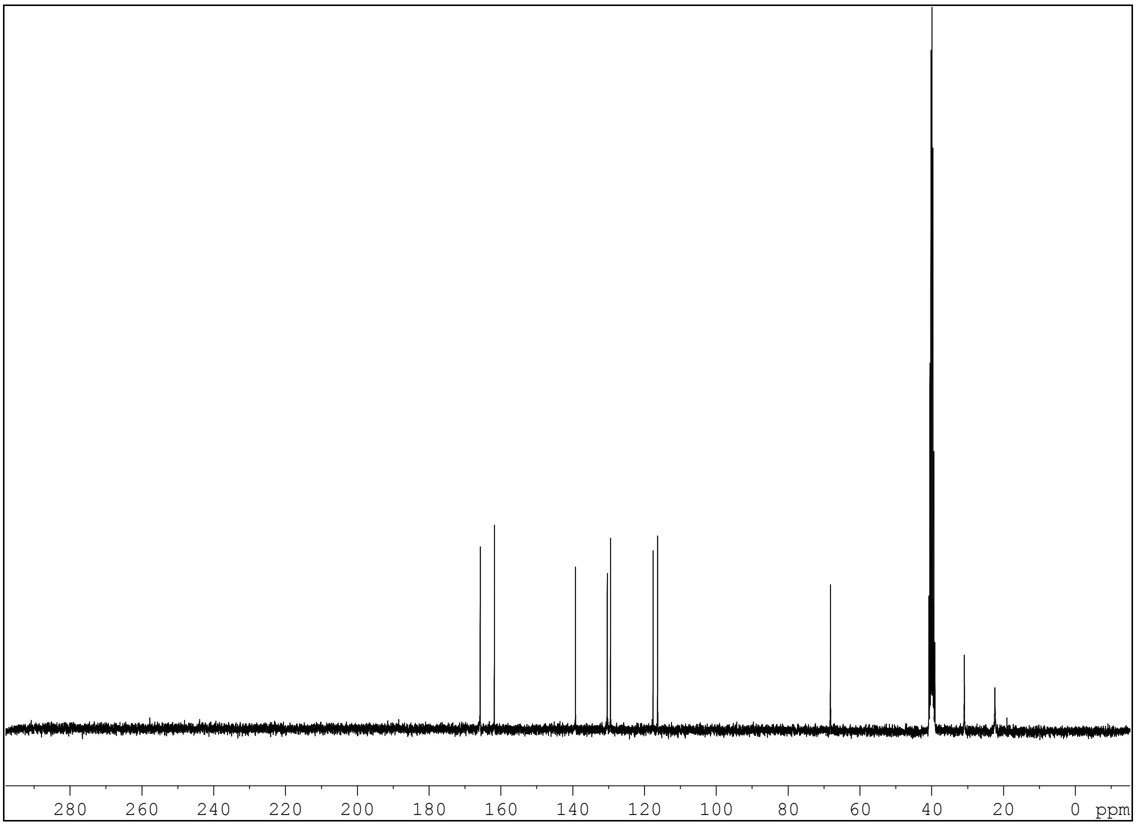


Figure 3.12a: ^{13}C-NMR Spectrum of **(IV)**.

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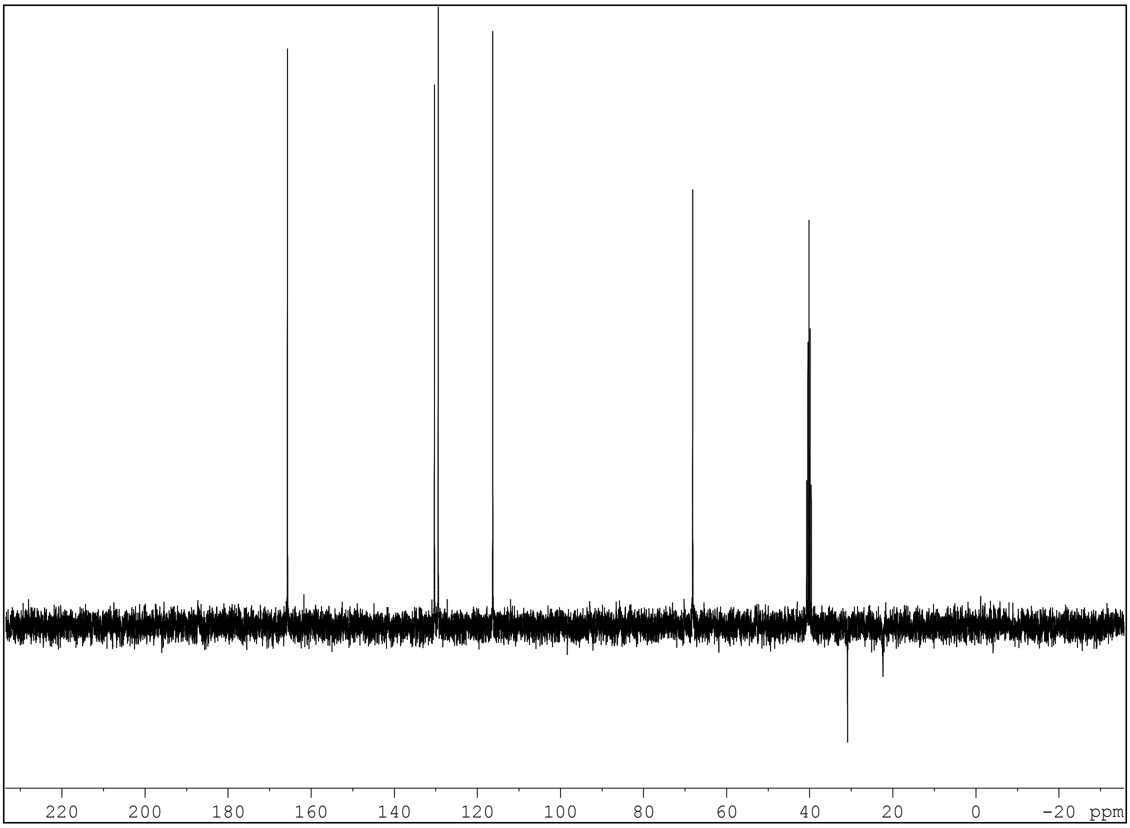


Figure 3.12b: DEPT-135-NMR Spectrum of **(IV)**.

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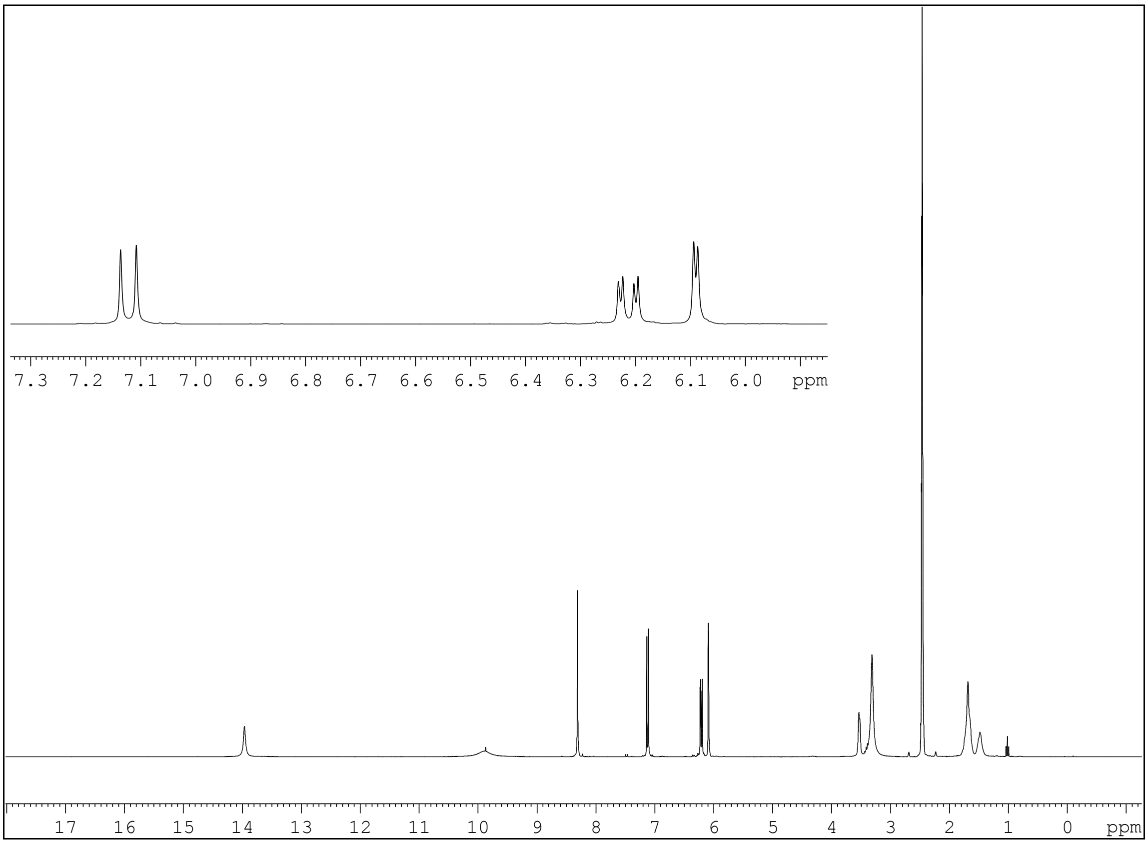


Figure 3.13: ^{1}H-NMR Spectrum of **(V)**.

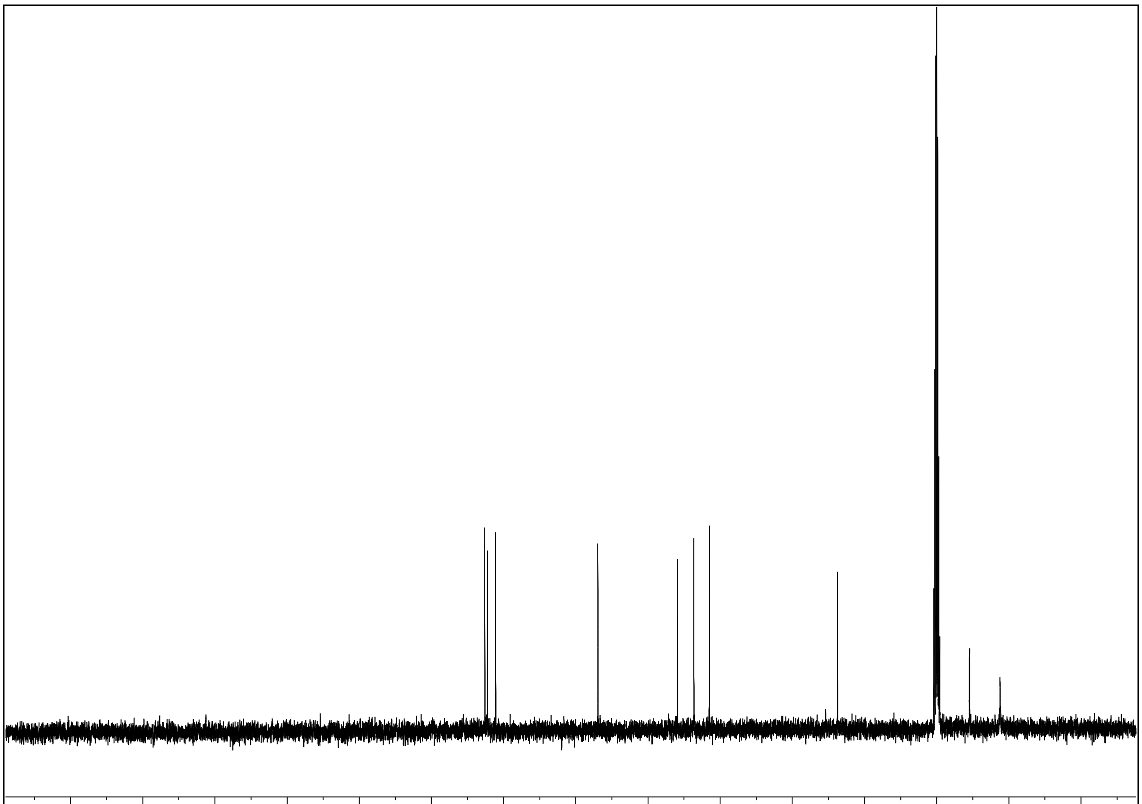


Figure 3.14a: ^{13}C-NMR Spectrum of **(V)**.

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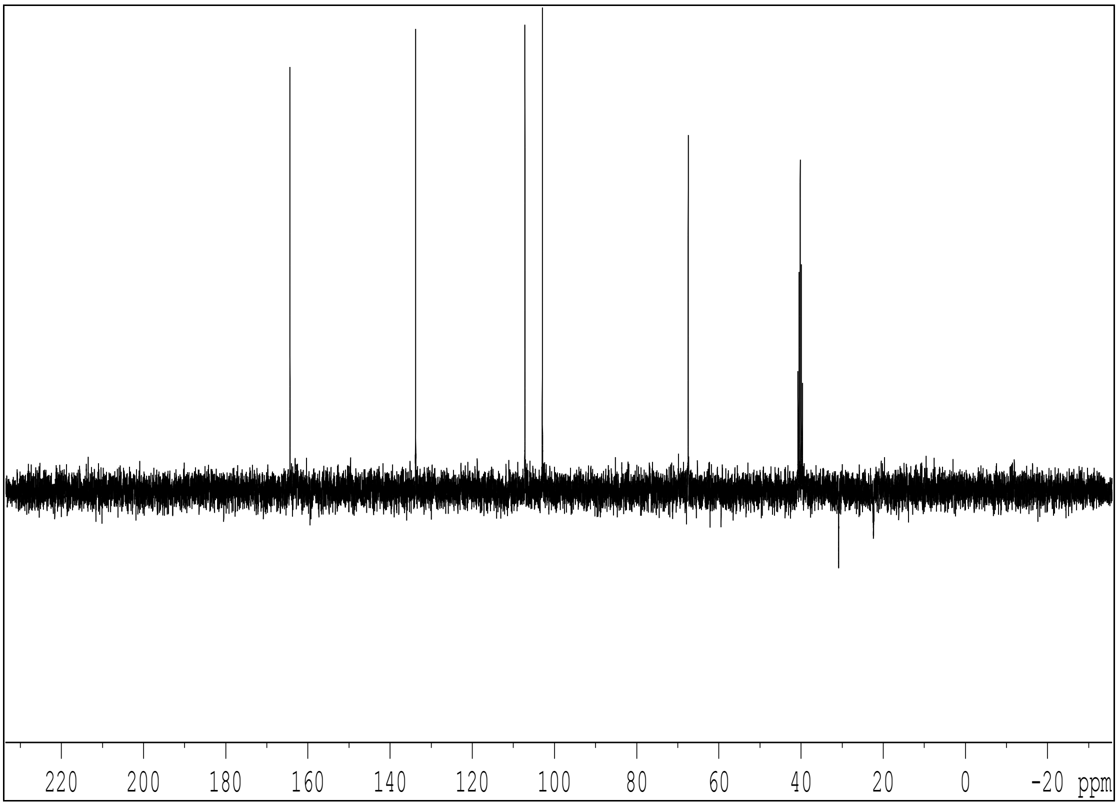


Figure 3.14b: DEPT -135-NMR Spectrum of **(V)**.

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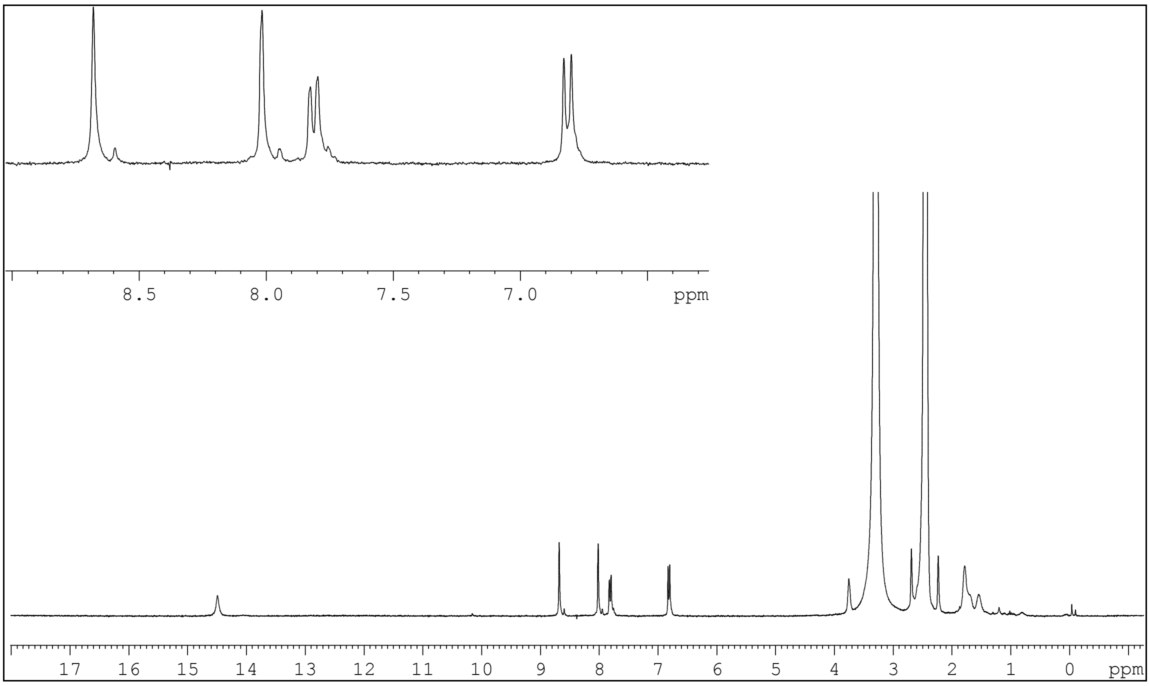


Figure 3.15: [1]H-NMR Spectrum of **(VI)**.

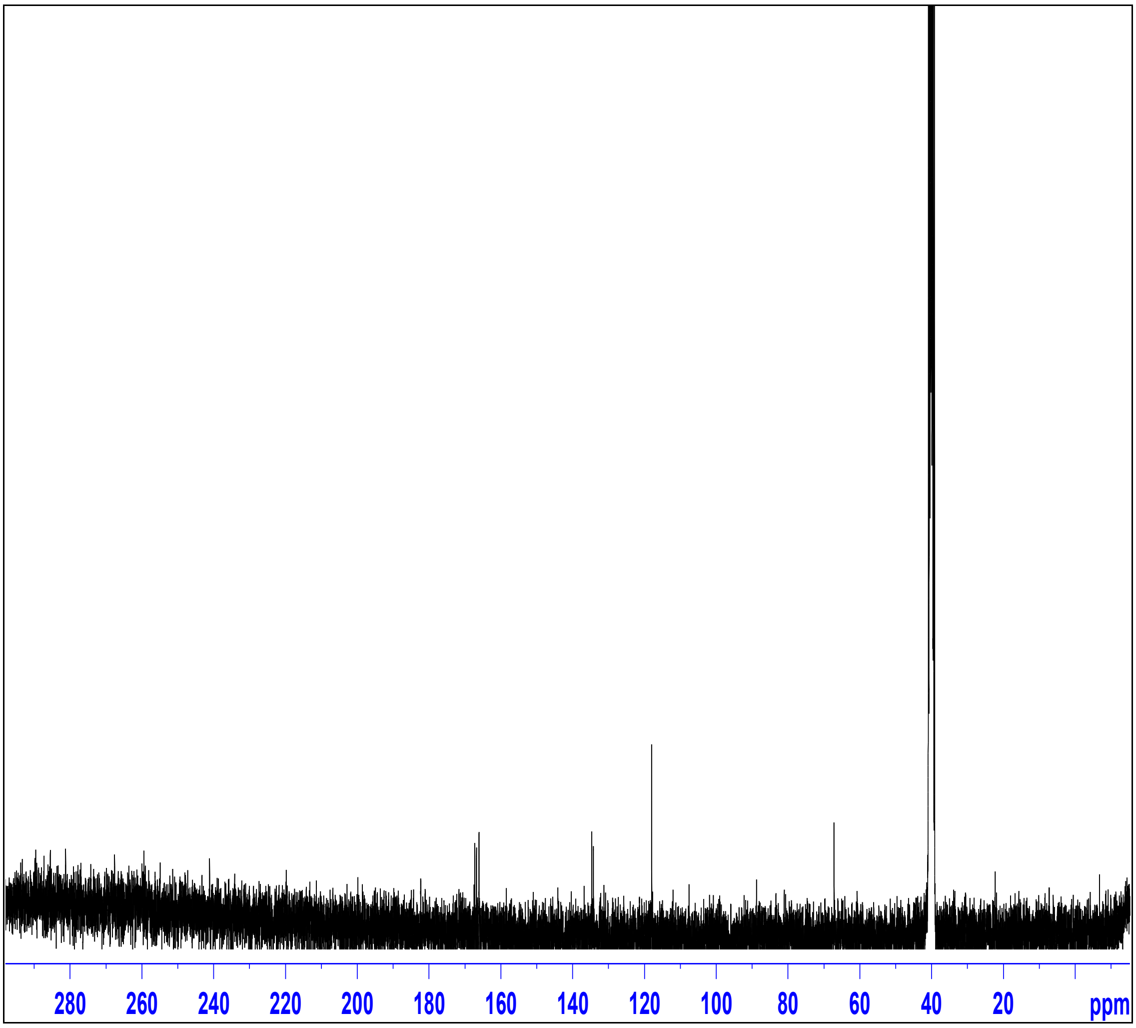


Figure 3.16: [13]C-NMR Spectrum of **(VI)**.

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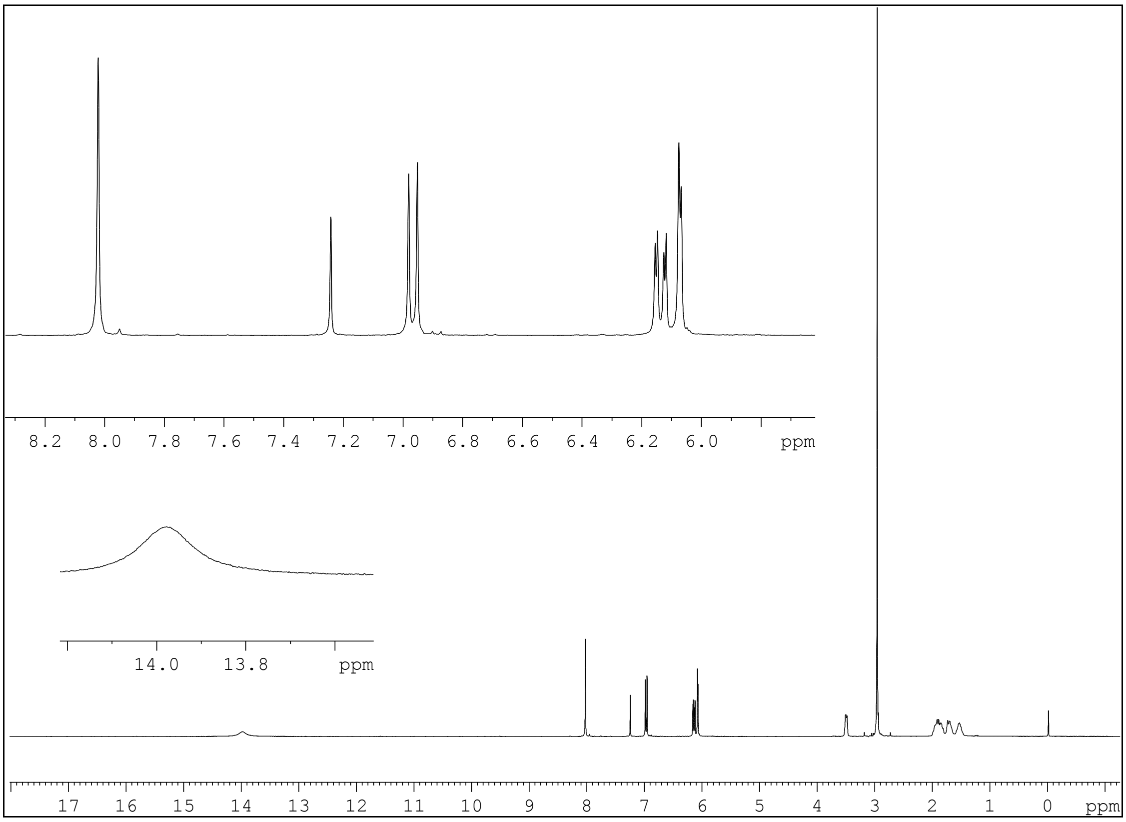


Figure 3.17: [1]H-NMR Spectrum of **(VII)**.

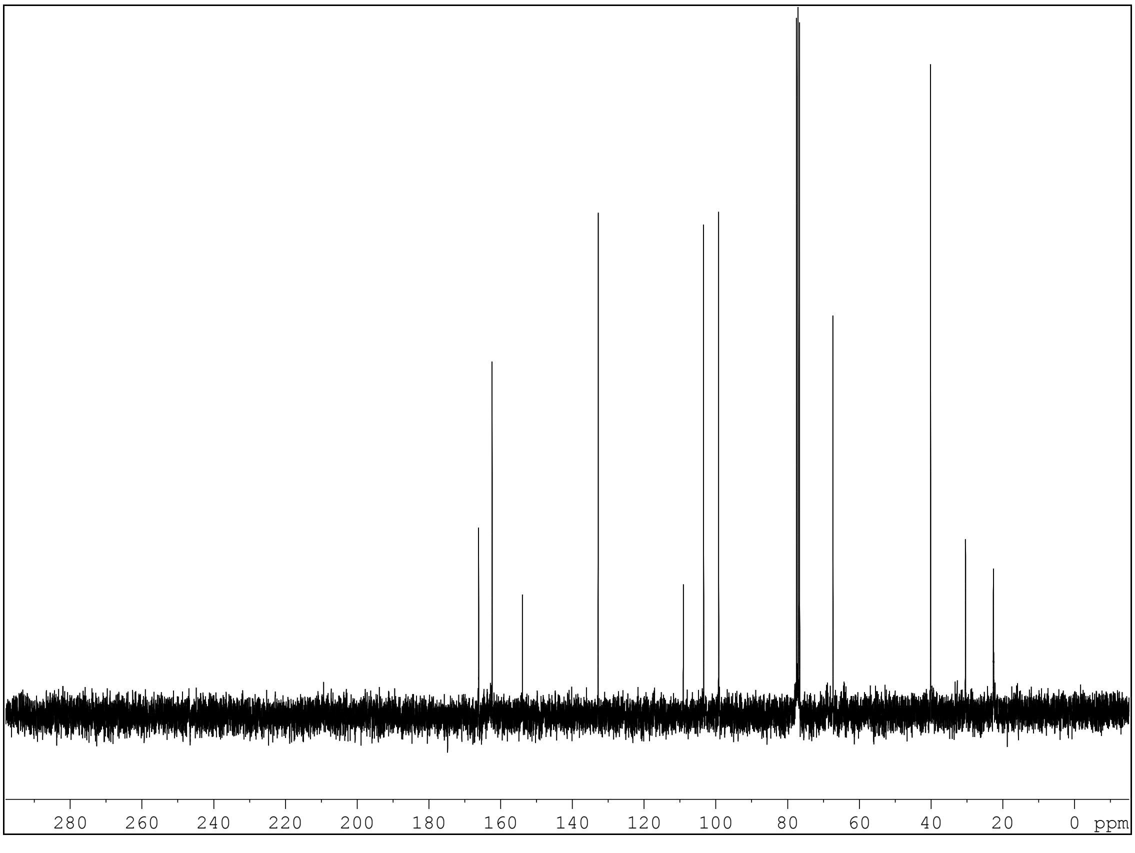


Figure 3.18a: [13]C-NMR Spectrum of **(VII)**.

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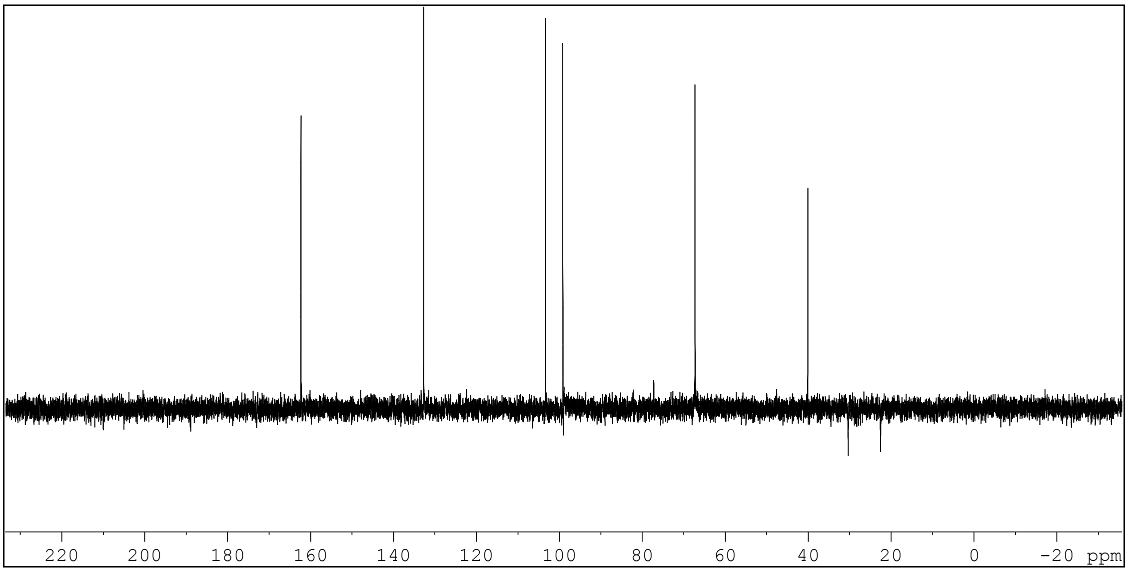


Figure 3.18b: DEPT-135-NMR Spectrum of **(VII)**.

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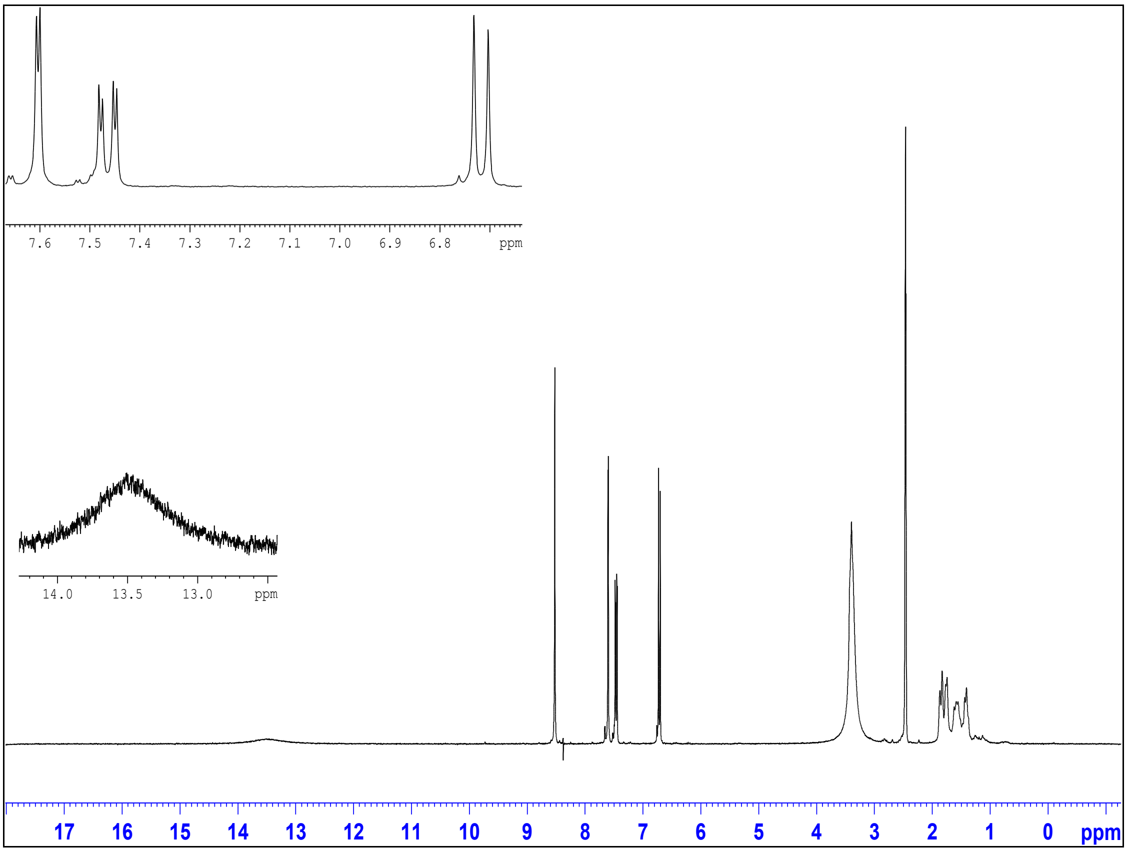


Figure 3.19: [1]H -NMR Spectrum of **(VIII)**.

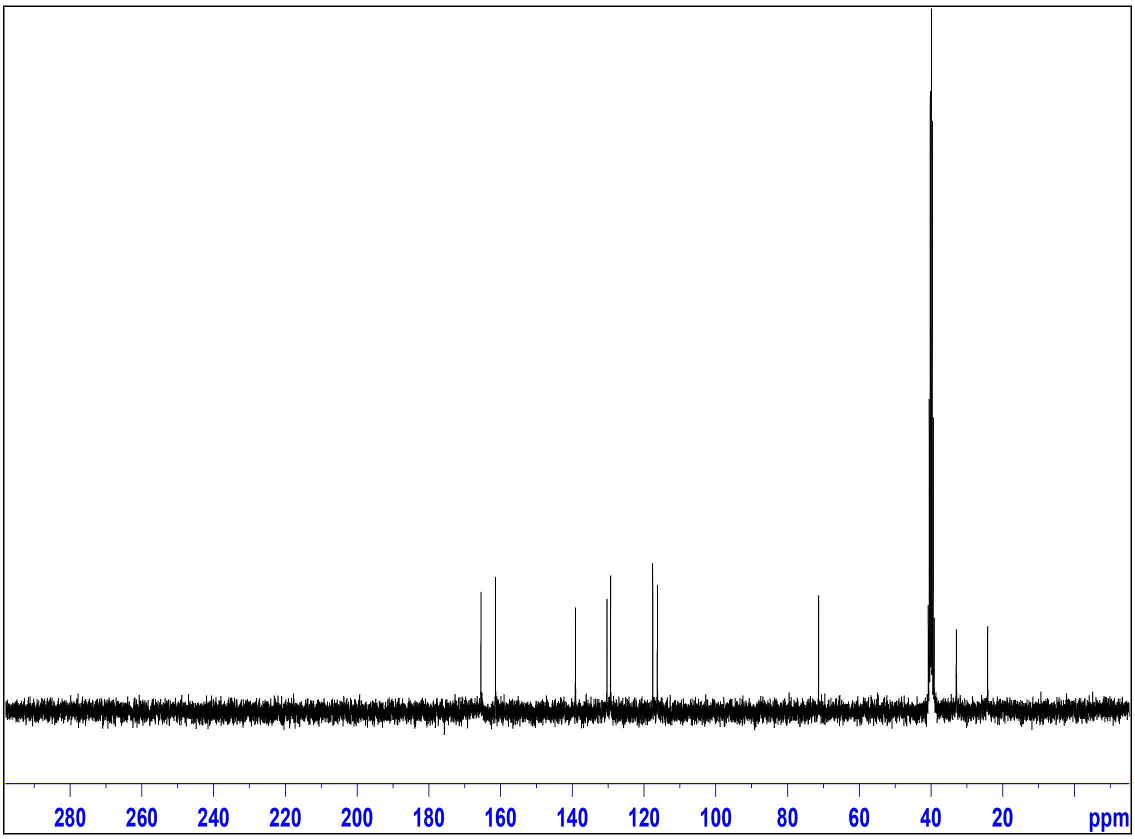


Figure 3.20: [13]C -NMR Spectrum of **(VIII)**.

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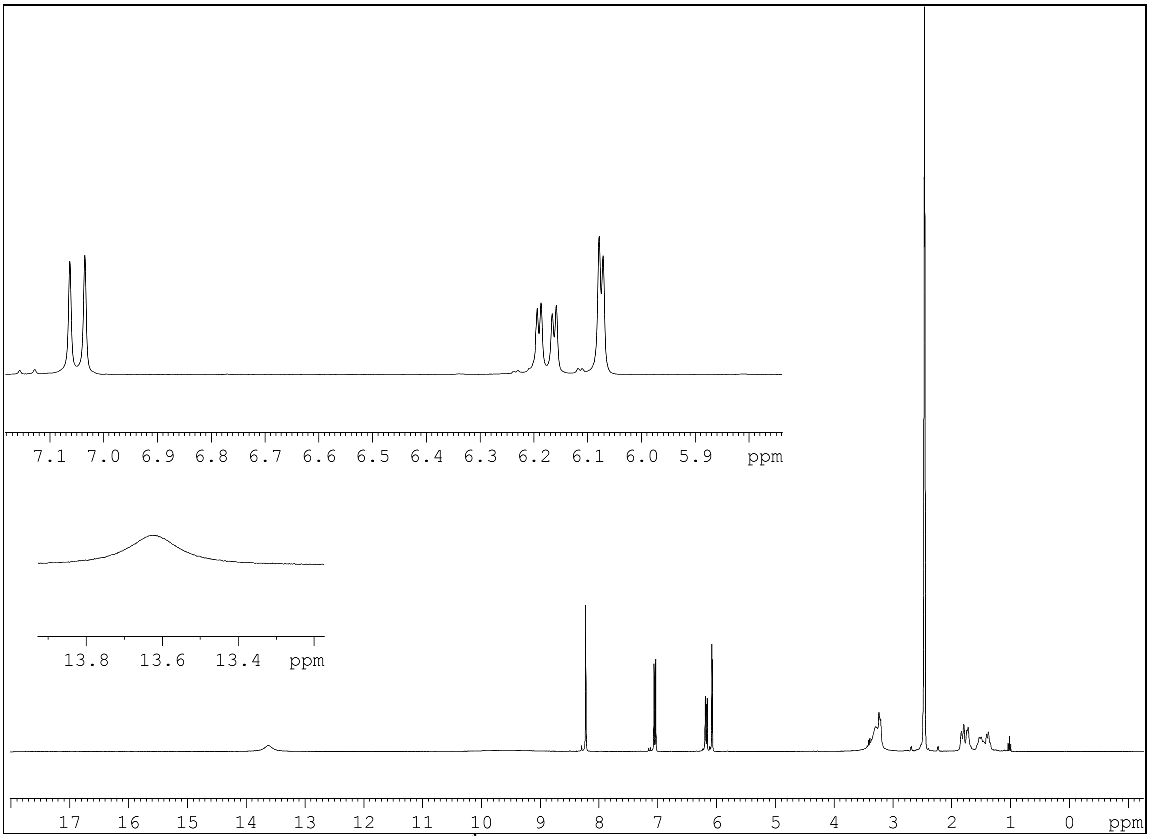


Figure 3.21: ^{1}H -NMR Spectrum of **(IX)**.

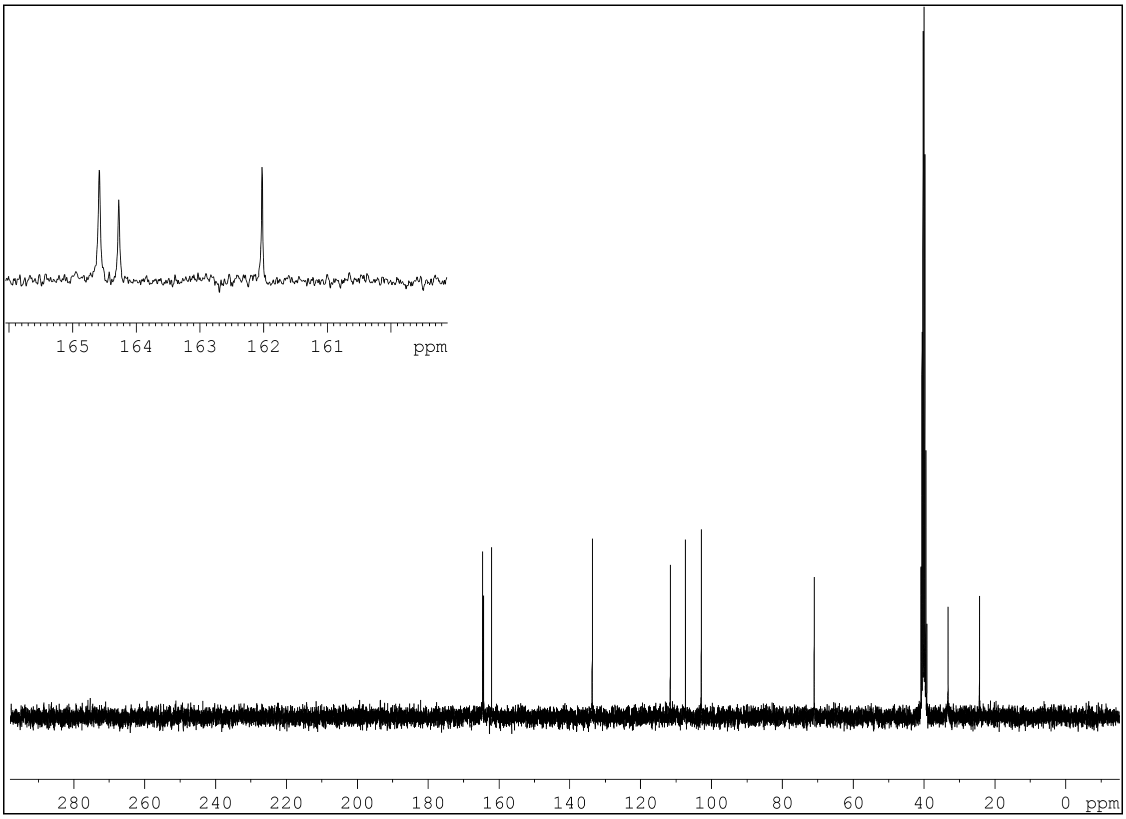


Figure 3.22a: ^{13}C -NMR Spectrum of **(IX)**.

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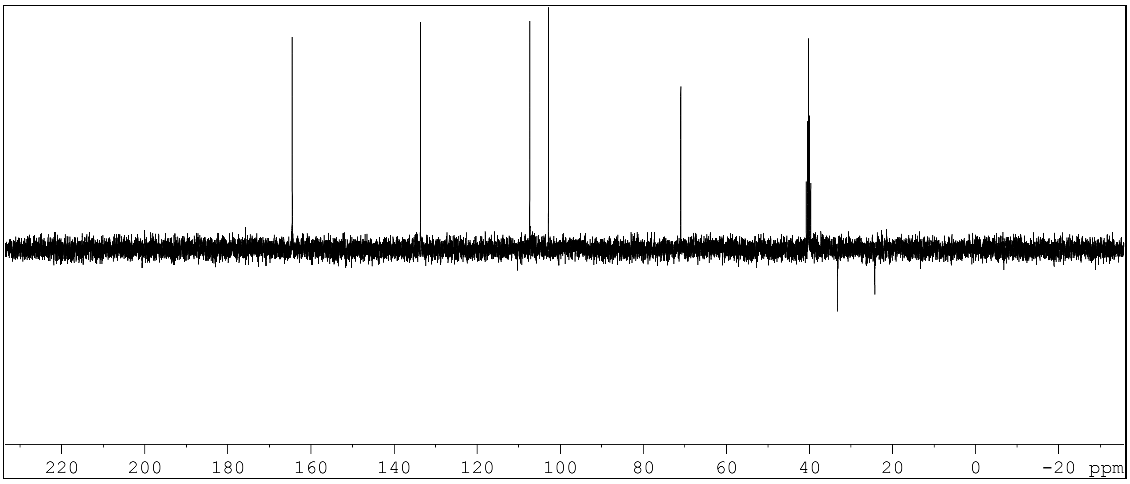


Figure 3.22b: DEPT-135-NMR Spectrum of **(IX)**.

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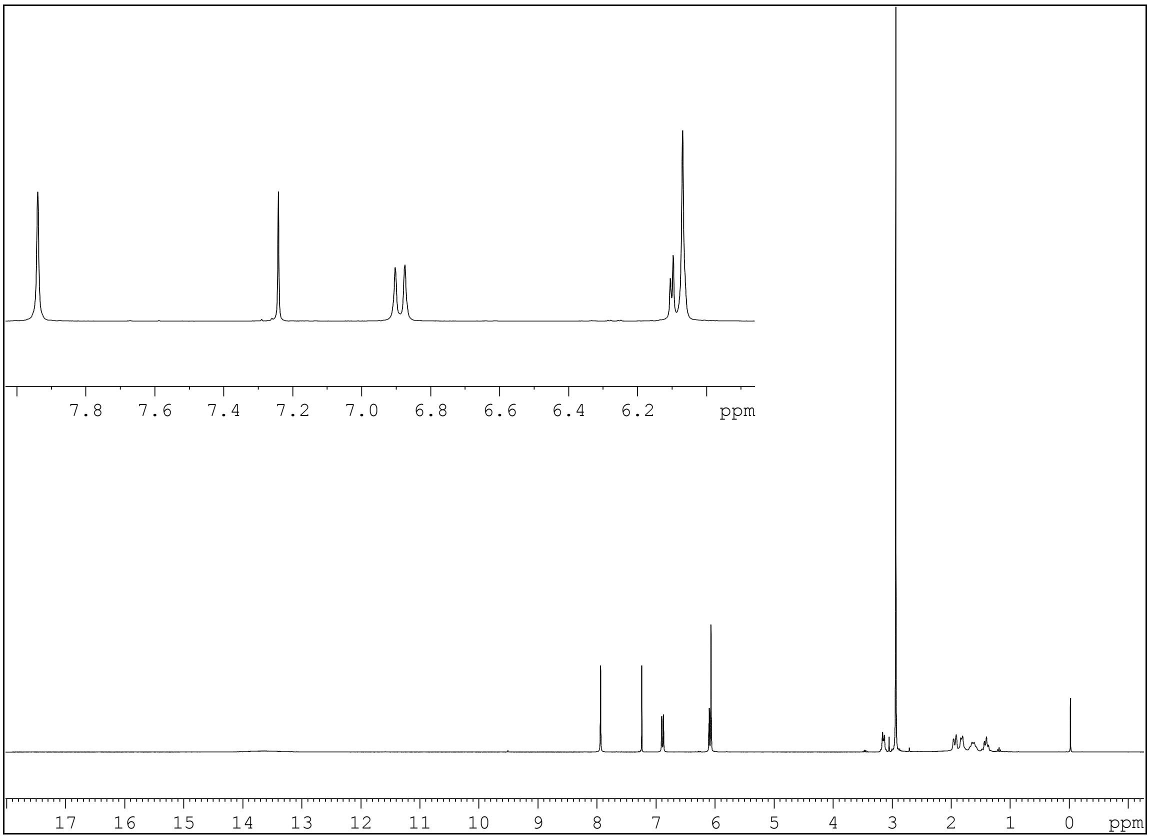


Figure 3.23: ^{1}H -NMR Spectrum of **(X)**.

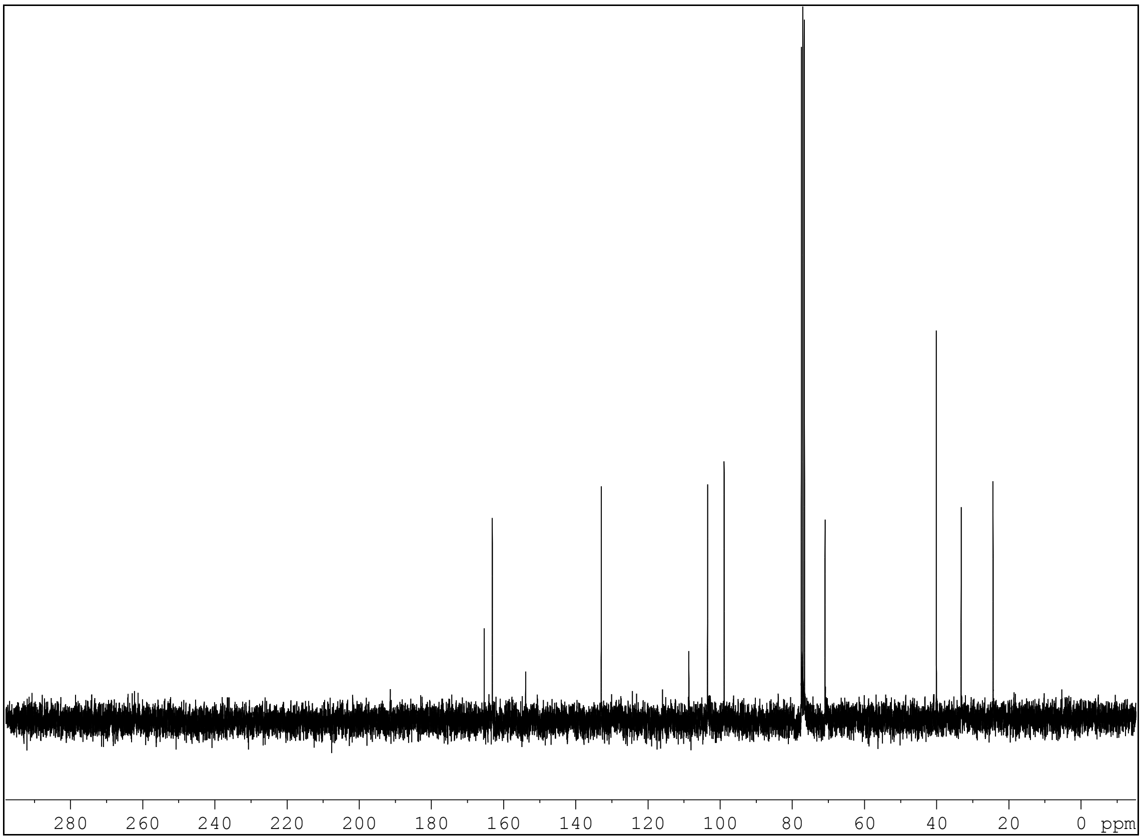


Figure 3.24a: ^{13}C -NMR Spectrum of **(X)**.

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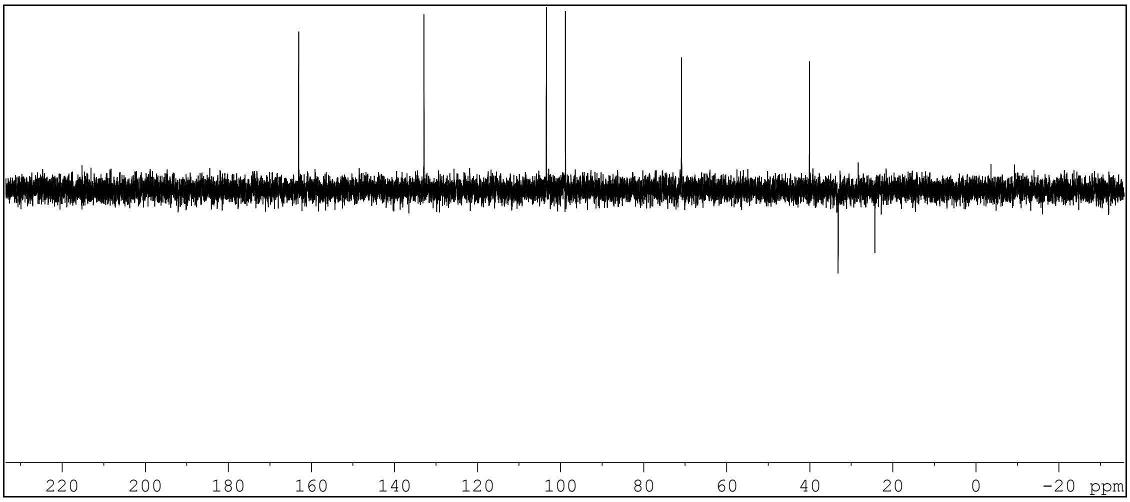


Figure 3.24b: DEPT-135-NMR Spectrum of **(X)**.

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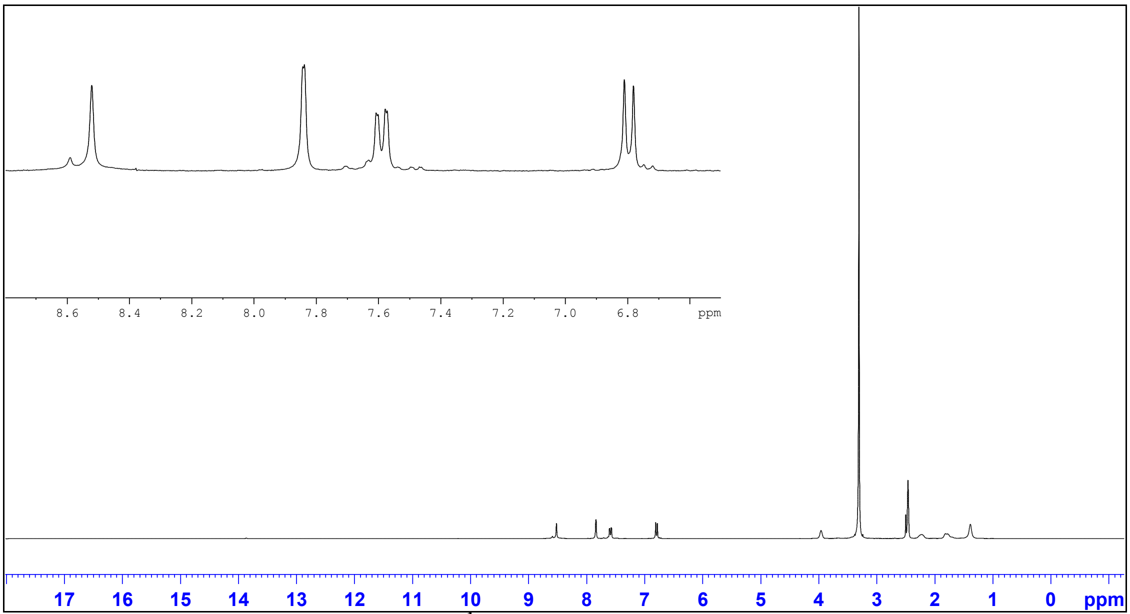


Figure 3.25: ^{1}H -NMR Spectrum of **(XI)**.

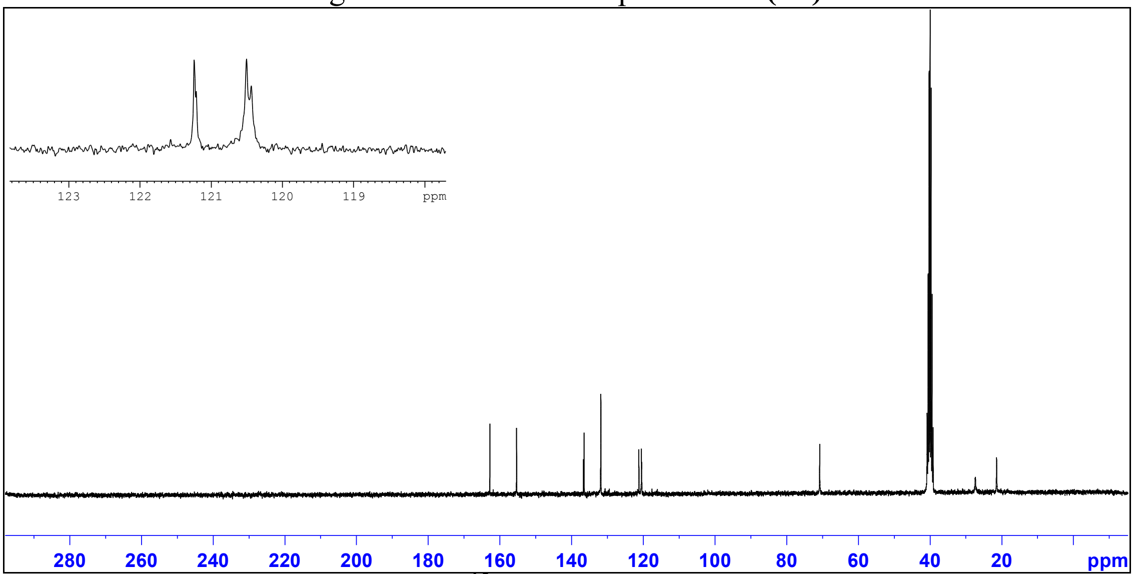


Figure 3.26a: ^{13}C -NMR Spectrum of **(XI)**.

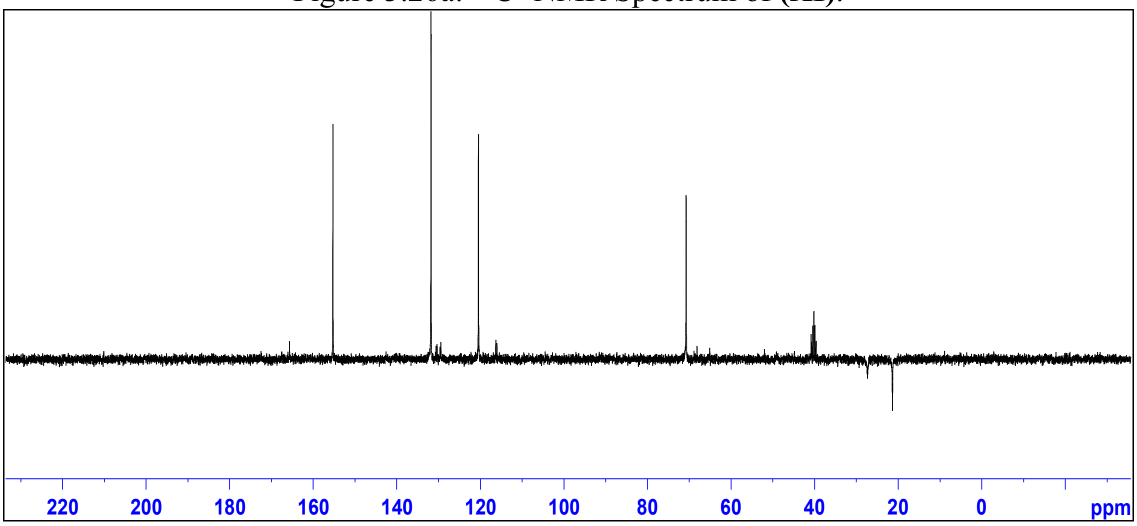


Figure 3.26b: DEPT-135-NMR Spectrum of **(XI)**.

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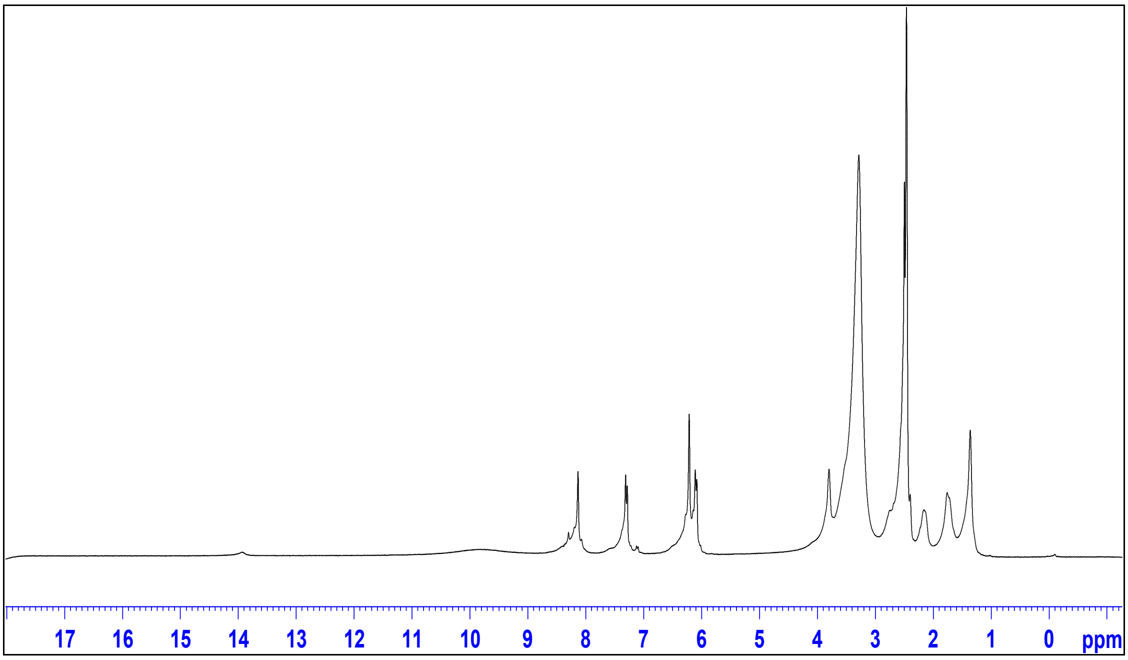


Figure 3.27: ^{1}H -NMR Spectrum of **(XII)**.

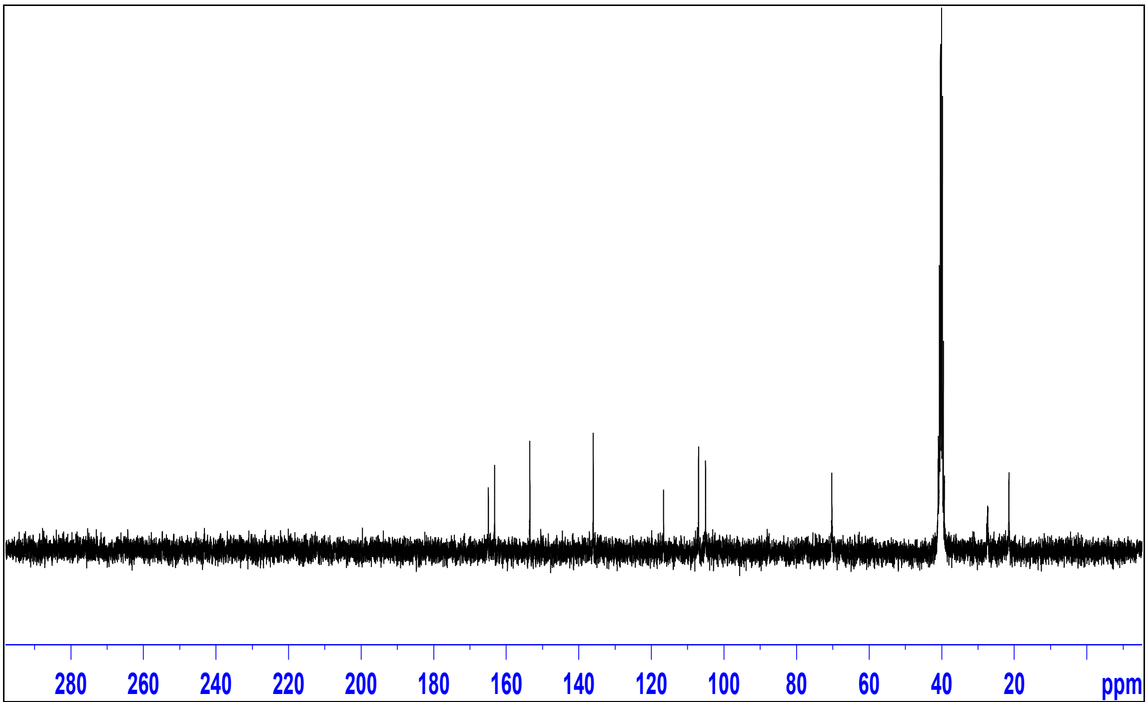


Figure 3.28: ^{13}C-NMR Spectrum of **(XII)**.

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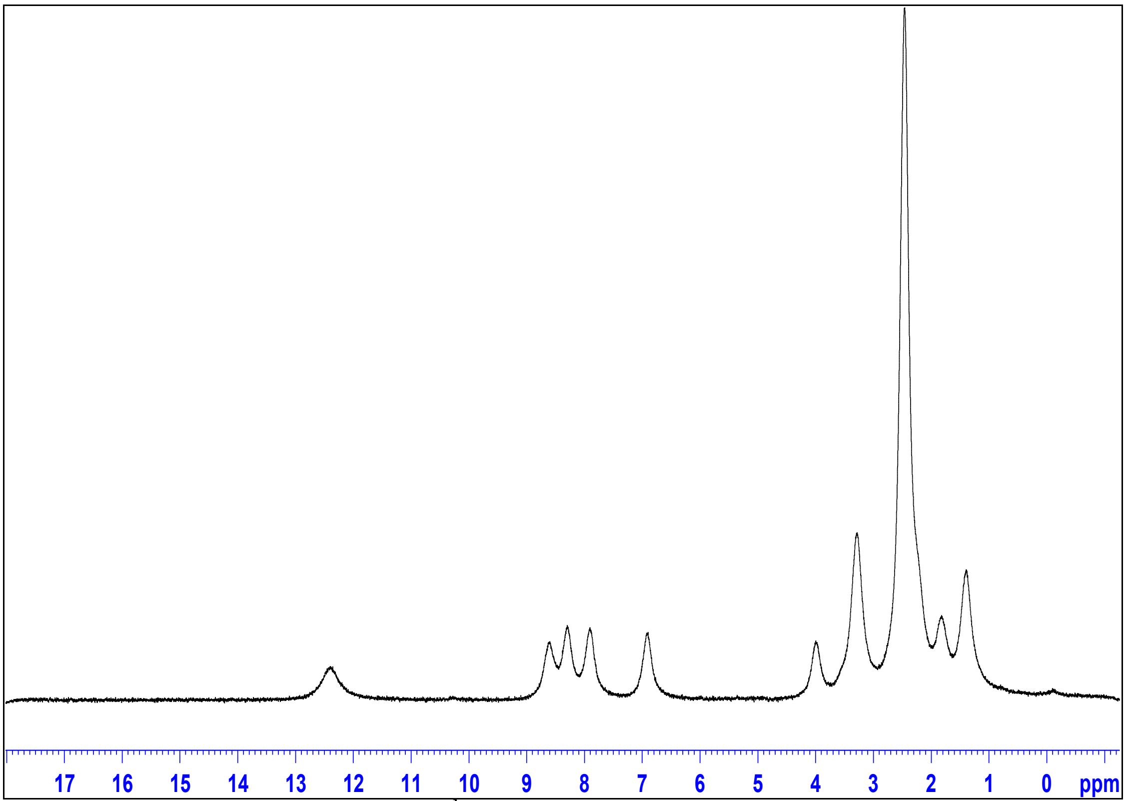


Figure 3.29: ^{1}H -NMR Spectrum of **(XIII)**.

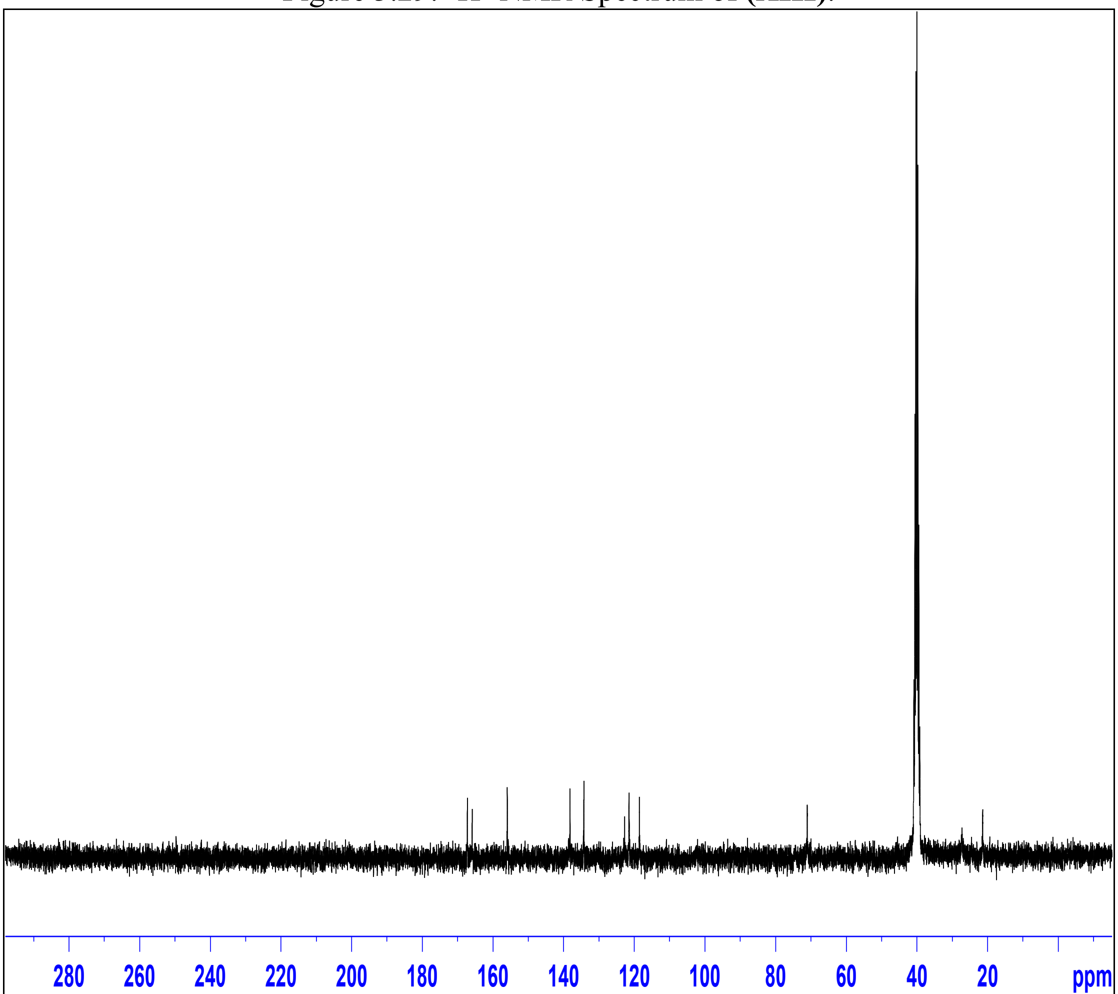


Figure 3.30: ^{13}C -NMR Spectrum of **(XIII)**.

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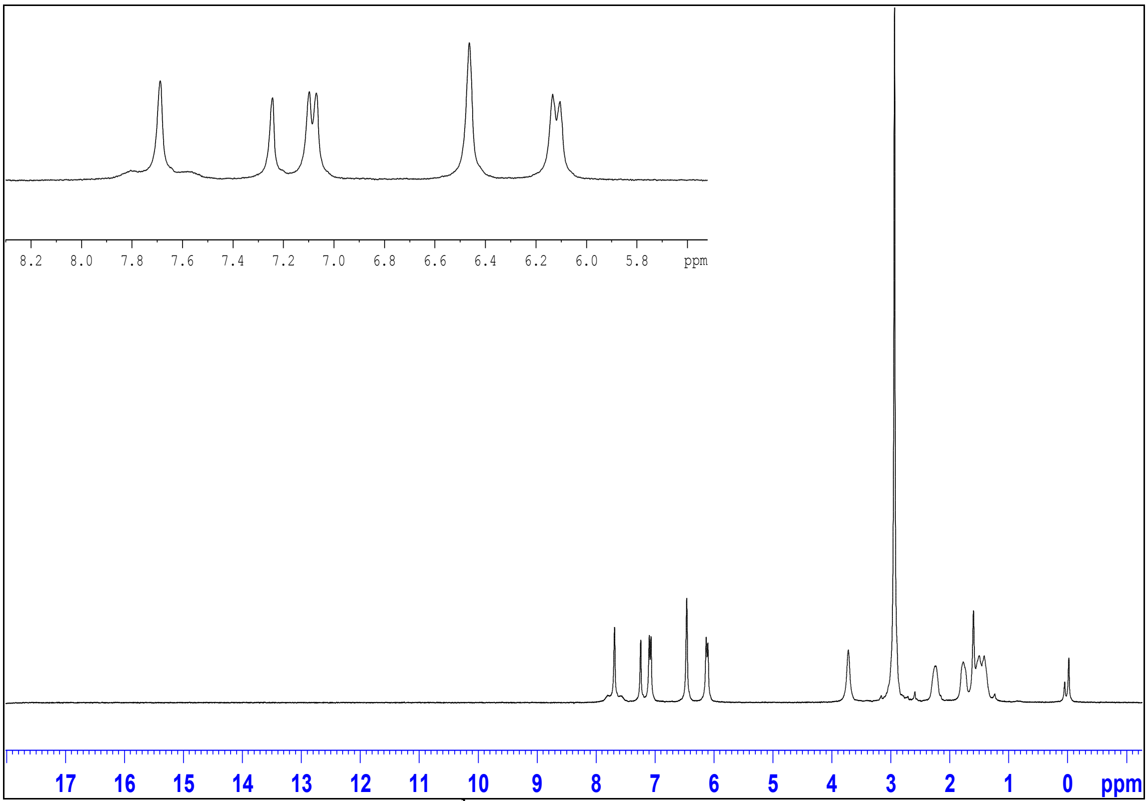


Figure 3.31: ^{1}H -NMR Spectrum of **(XIV)**.

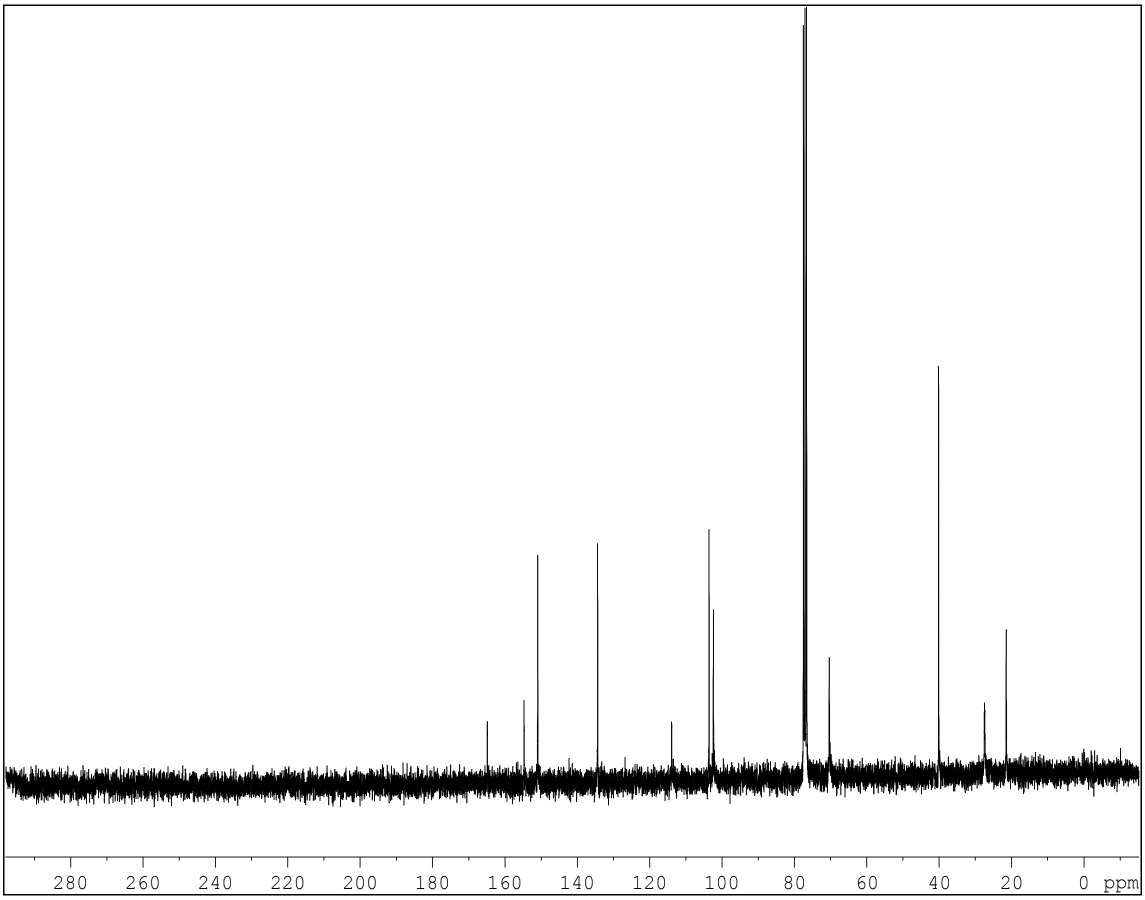


Figure 3.32a: ^{13}C -NMR Spectrum of **(XIV)**.

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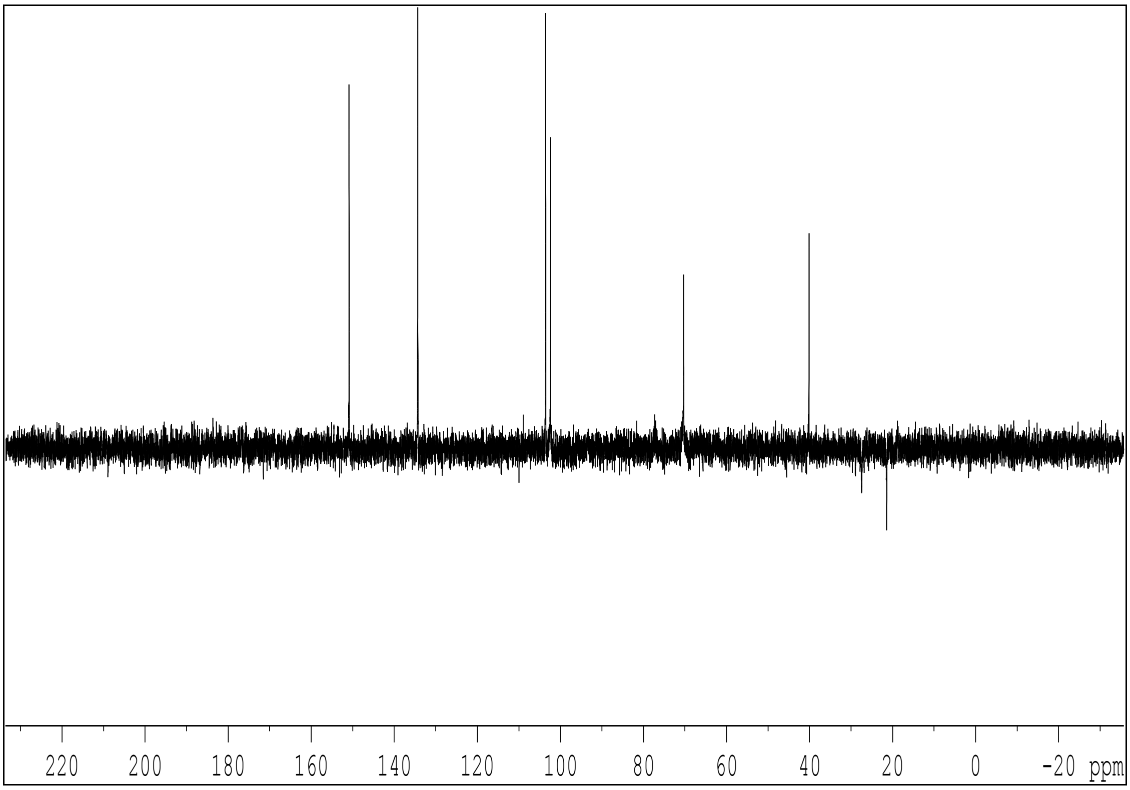


Figure 3.32b: DEPT-135-NMR Spectrum of **(XIV)**.

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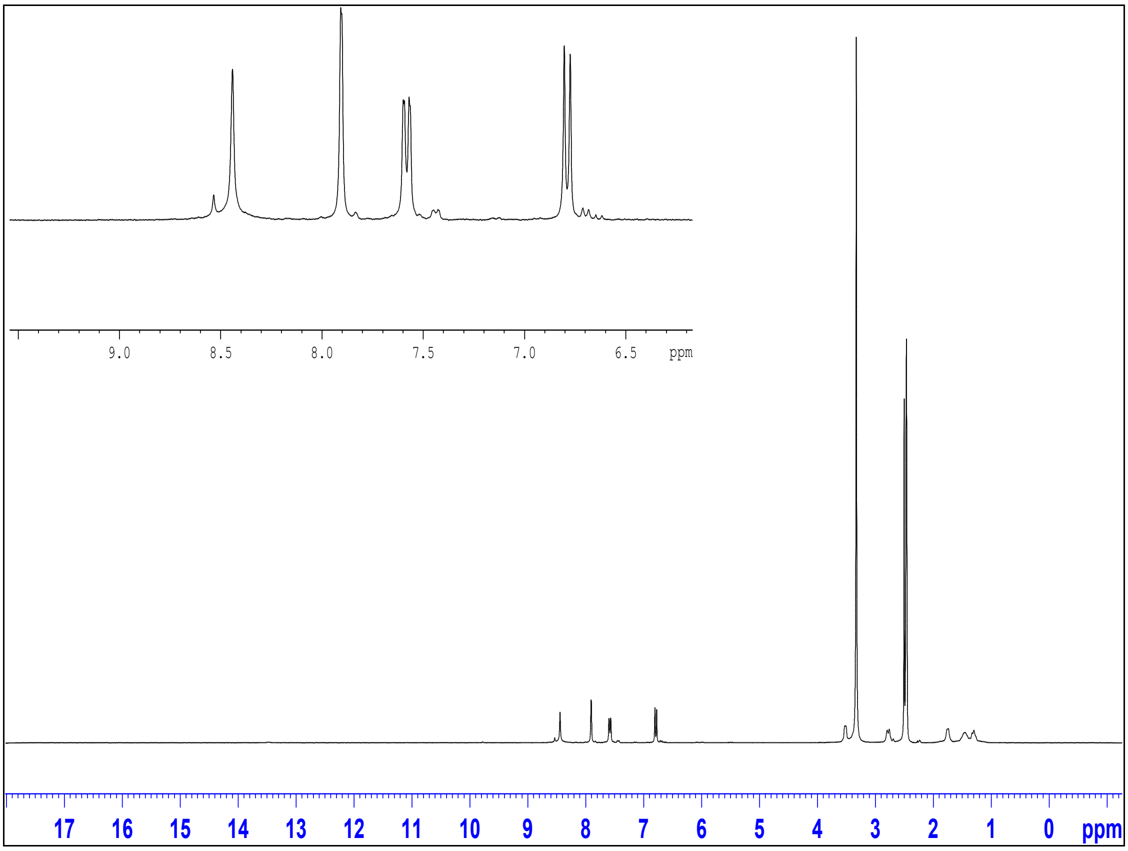


Figure 3.33: ^{1}H -NMR Spectrum of **(XV)**.

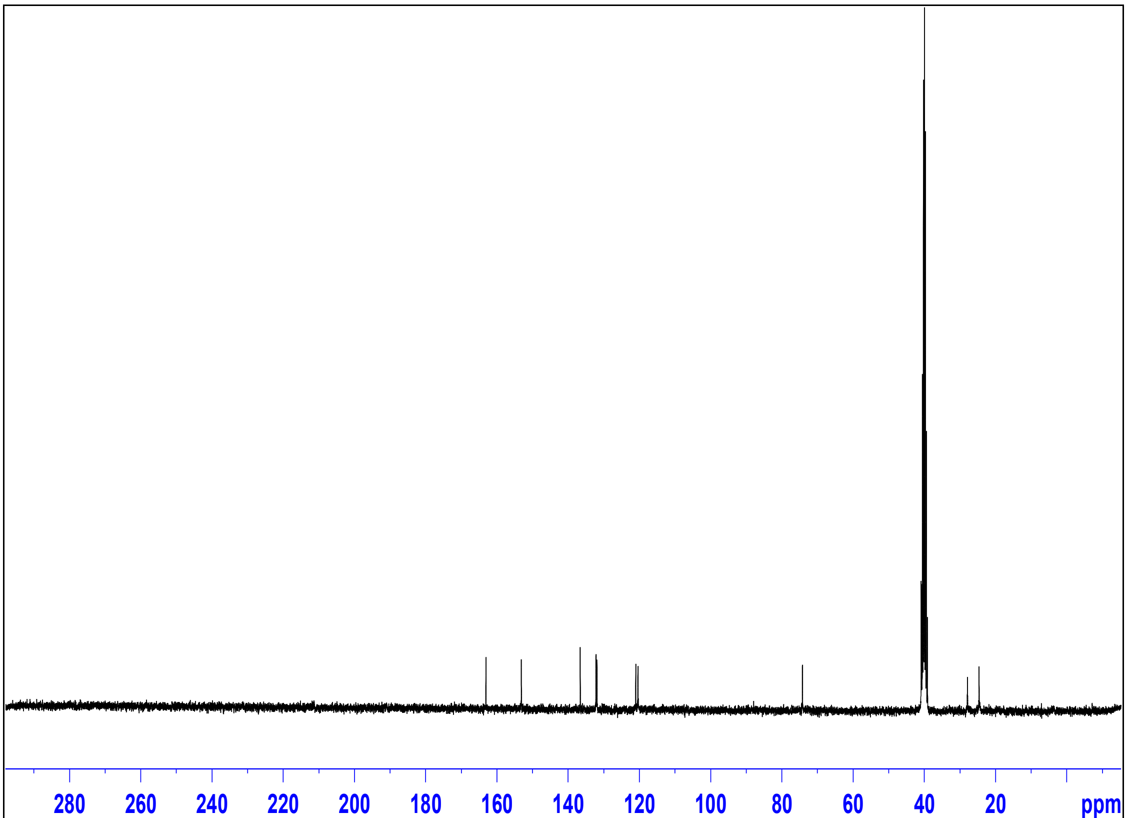


Figure 3.34: ^{13}C -NMR Spectrum of **(XV)**.

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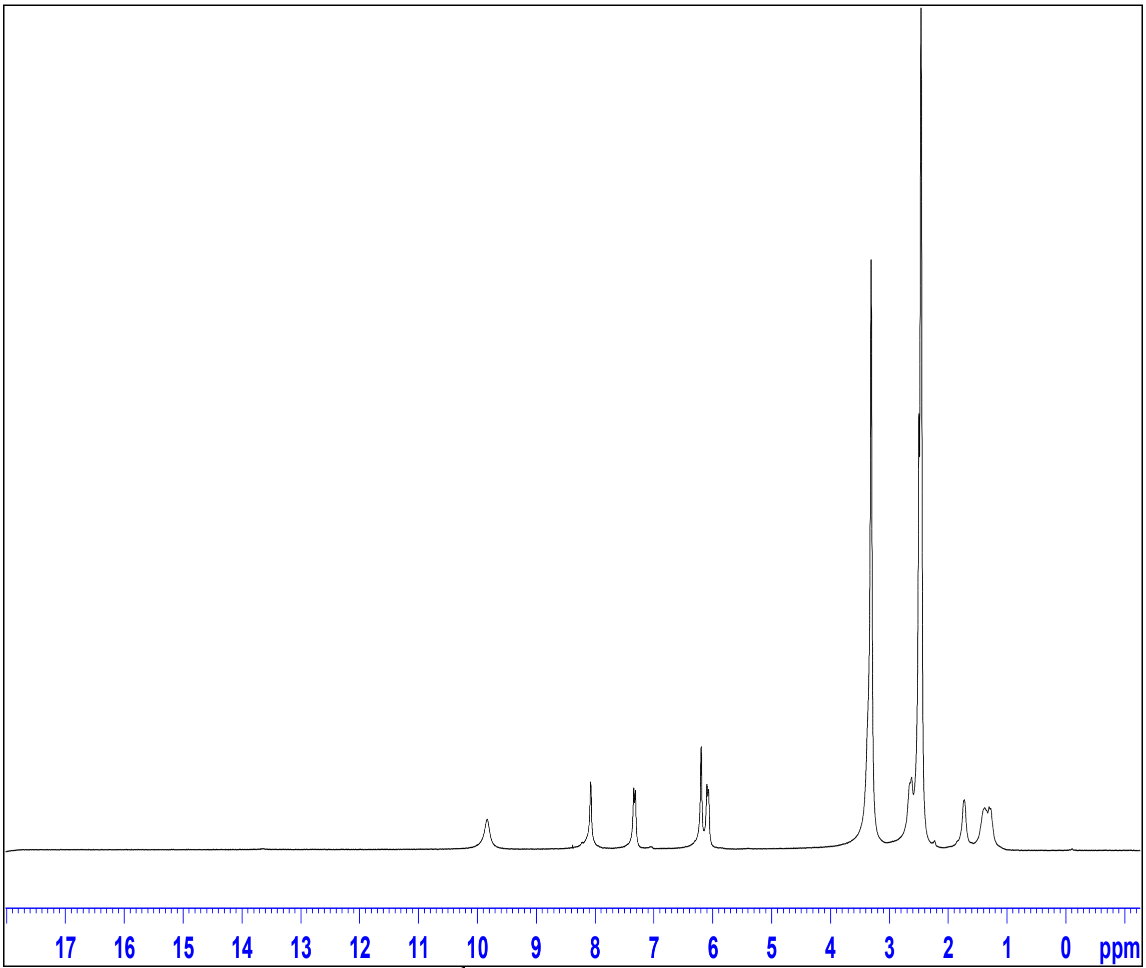


Figure 3.35: ^{1}H -NMR Spectrum of **(XVI)**.

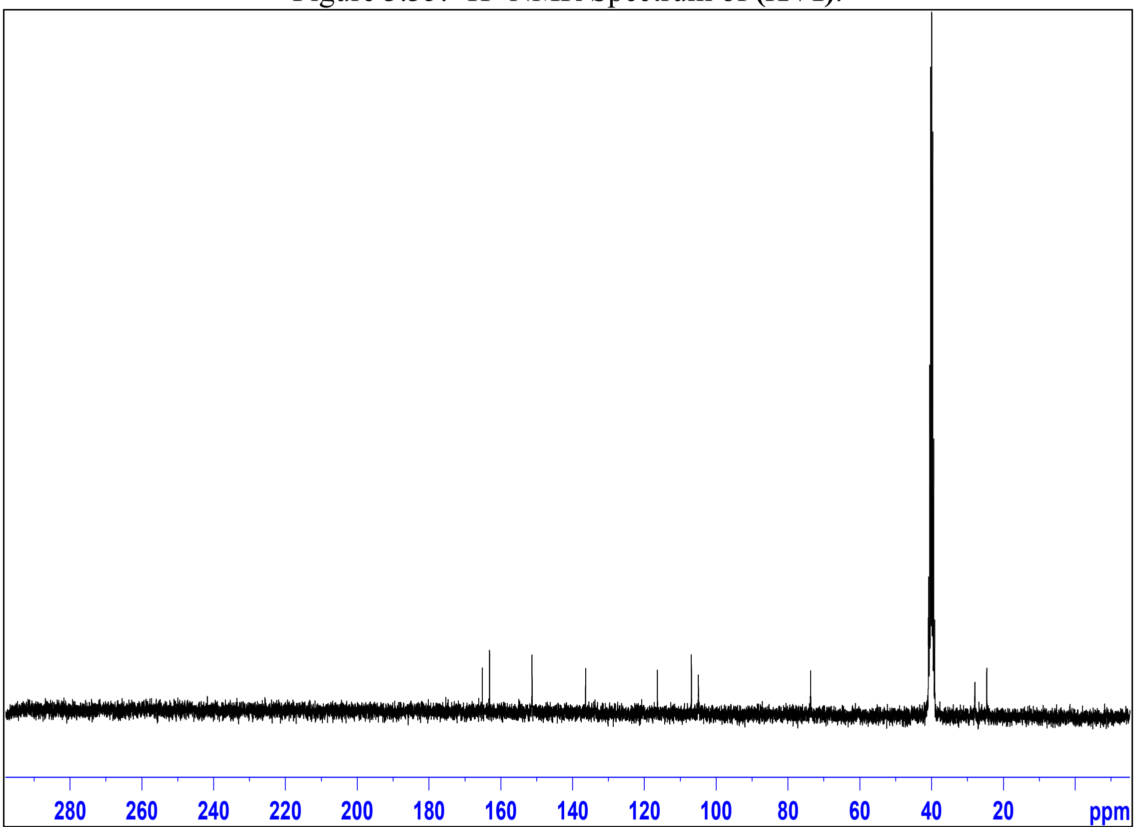


Figure 3.36: ^{13}C -NMR Spectrum of **(XVI)**.

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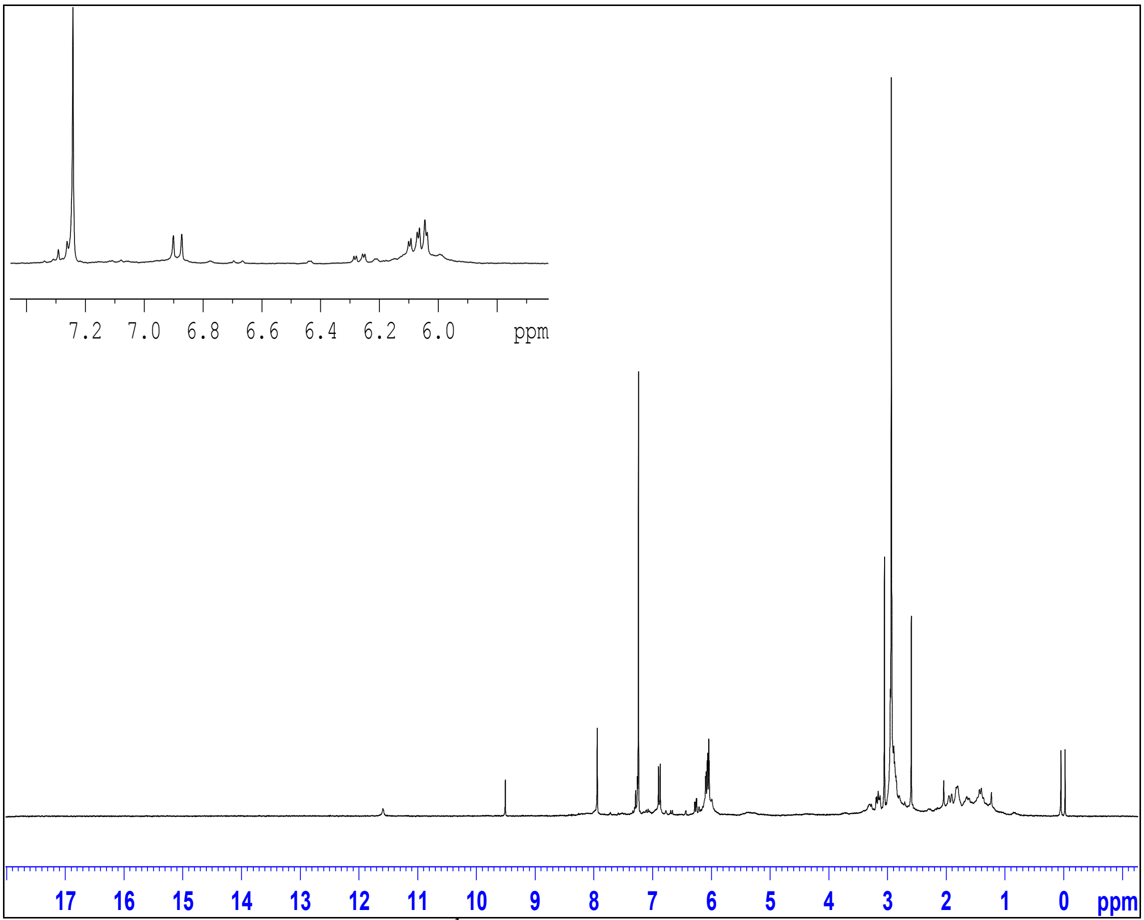


Figure 3.37: ^{1}H -NMR Spectrum of **(XVII)**.

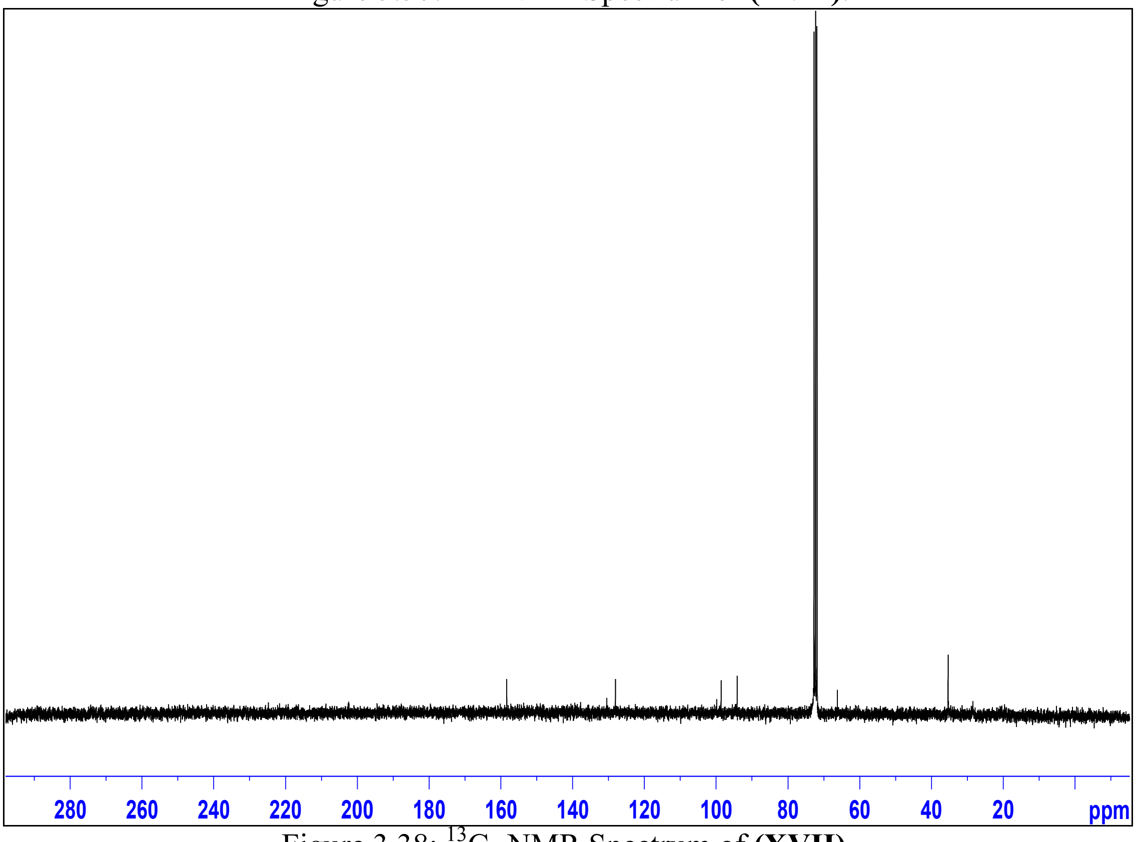


Figure 3.38: ^{13}C -NMR Spectrum of **(XVII)**.

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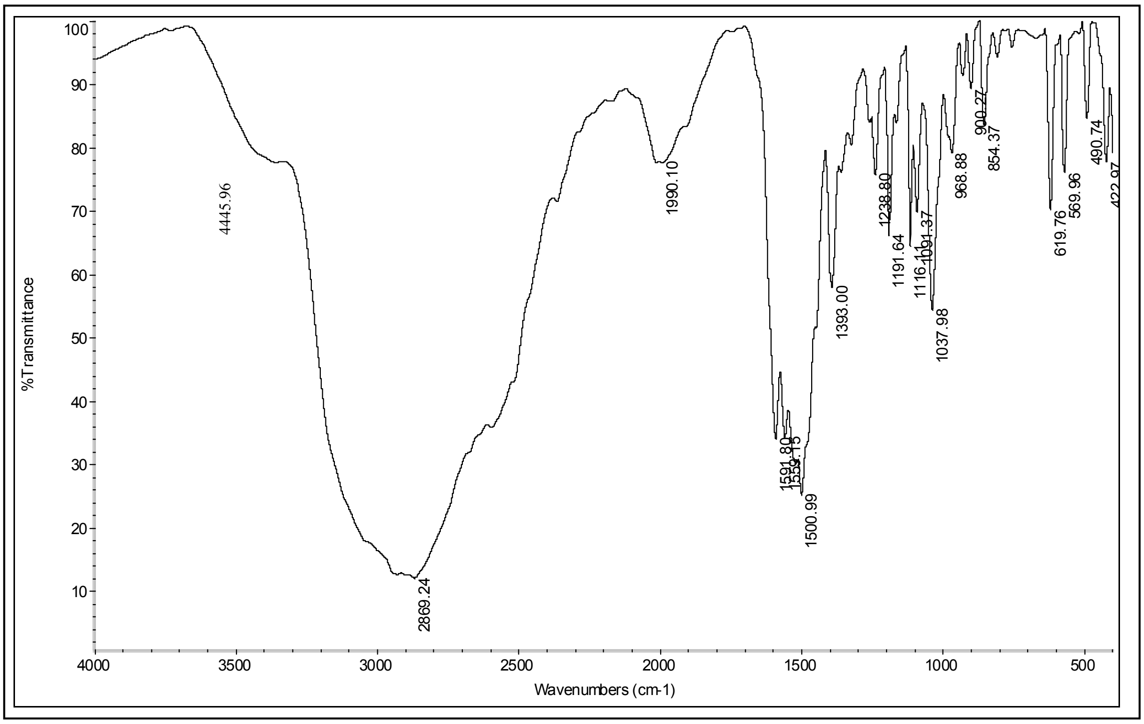


Figure 3.39: IR Spectra of *cis*-DACH.2HCl

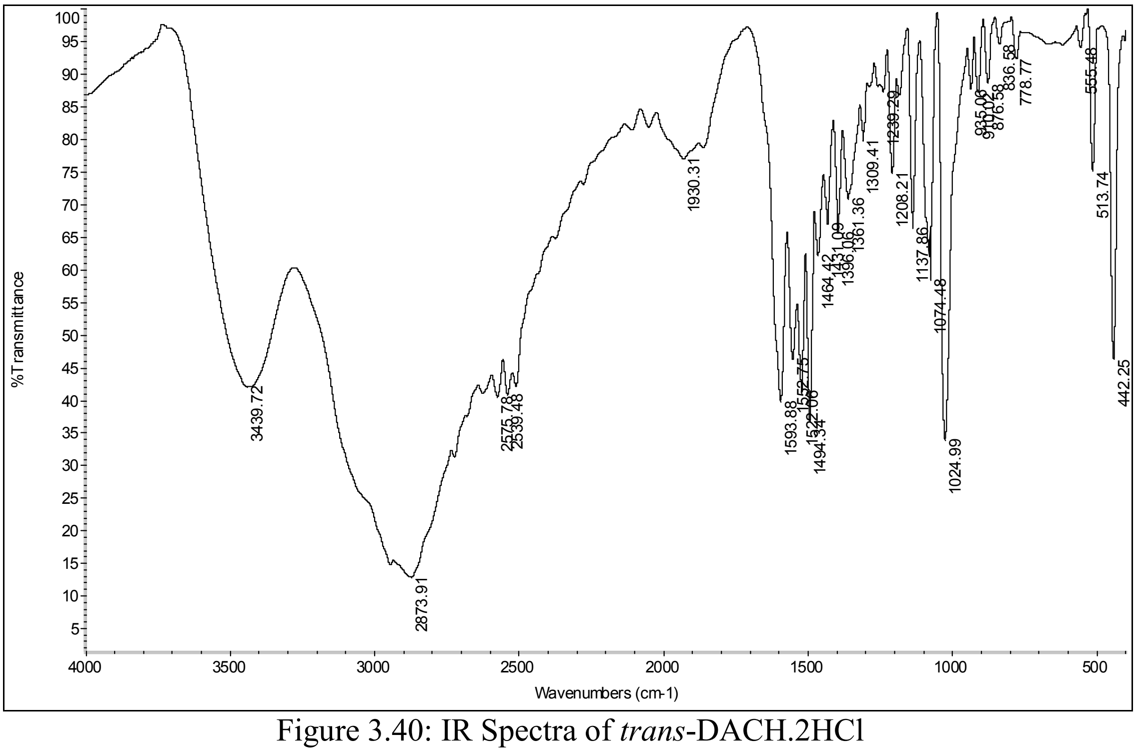


Figure 3.40: IR Spectra of *trans*-DACH.2HCl

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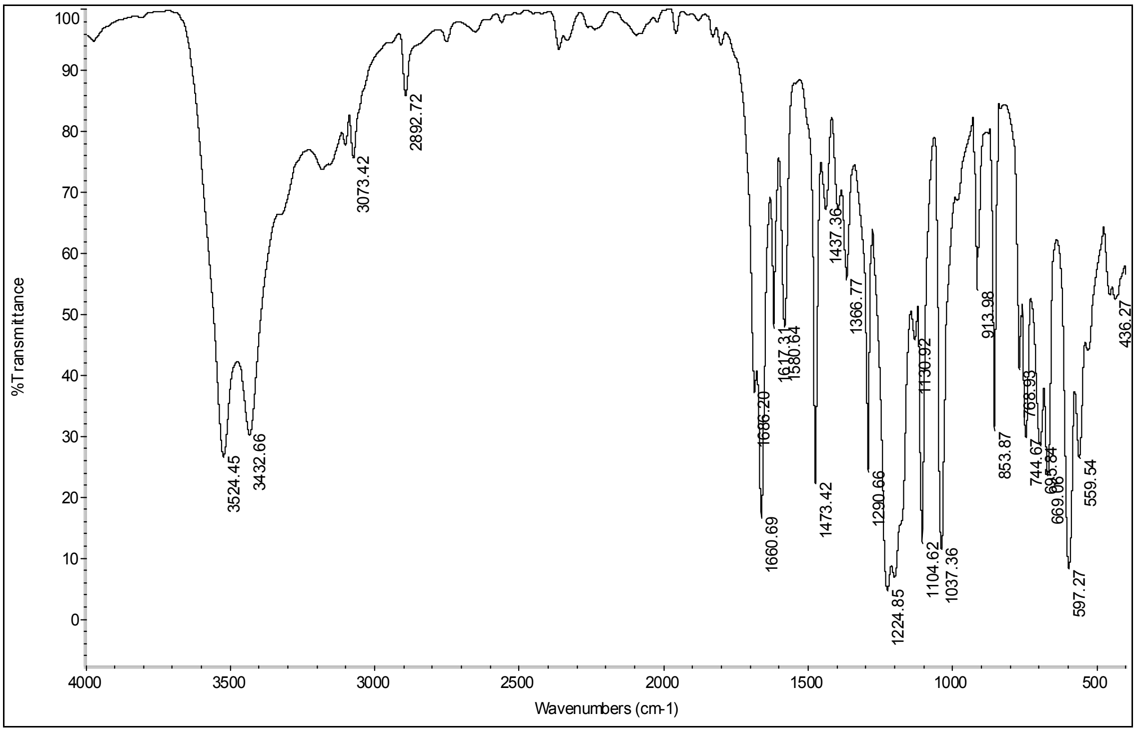


Figure 3.41: IR Spectra of **(I)**

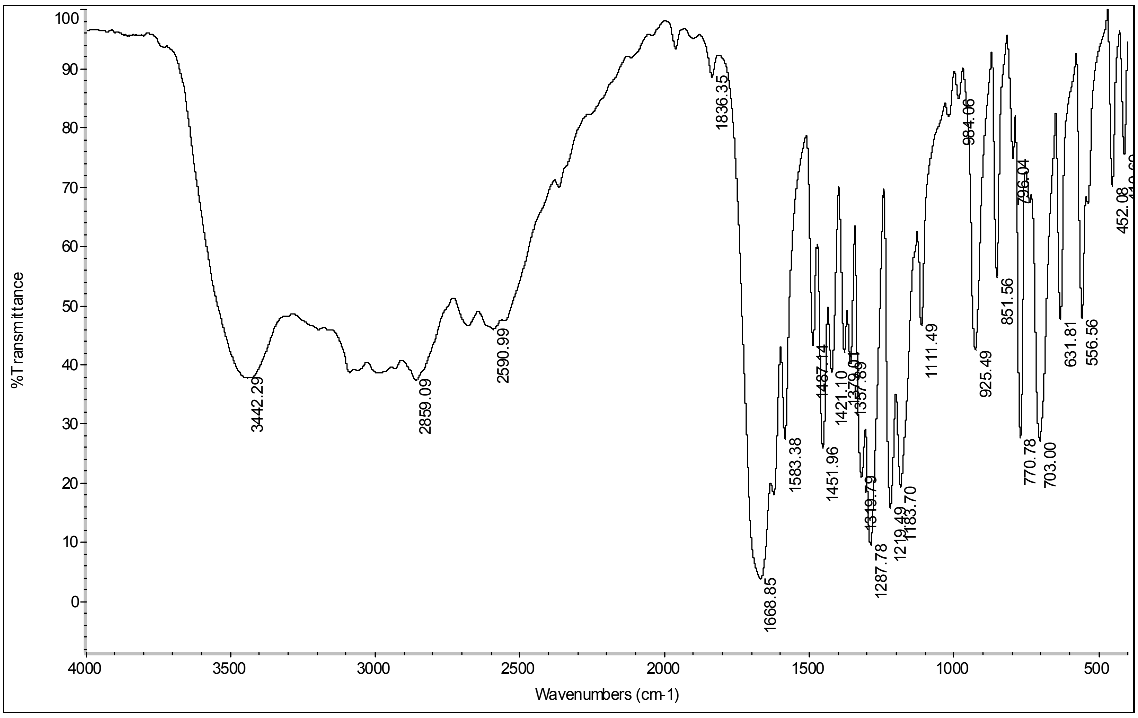


Figure 3.42: IR Spectra of **(II)**

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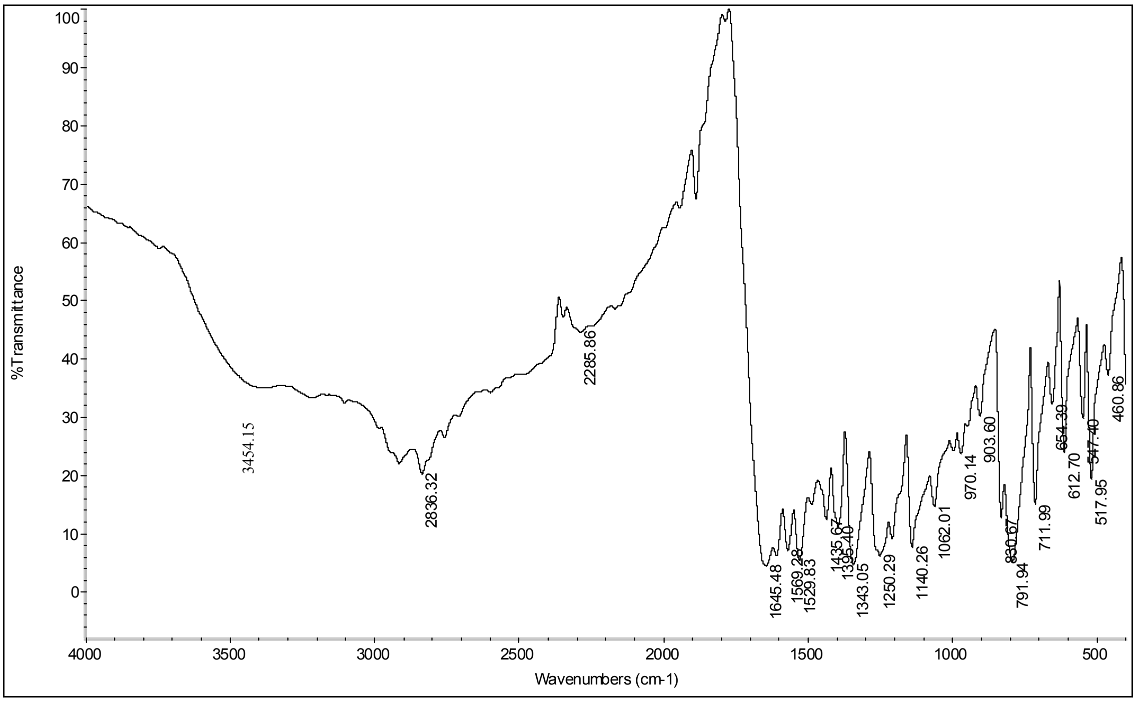


Figure 3.43: IR Spectra of **(III)**

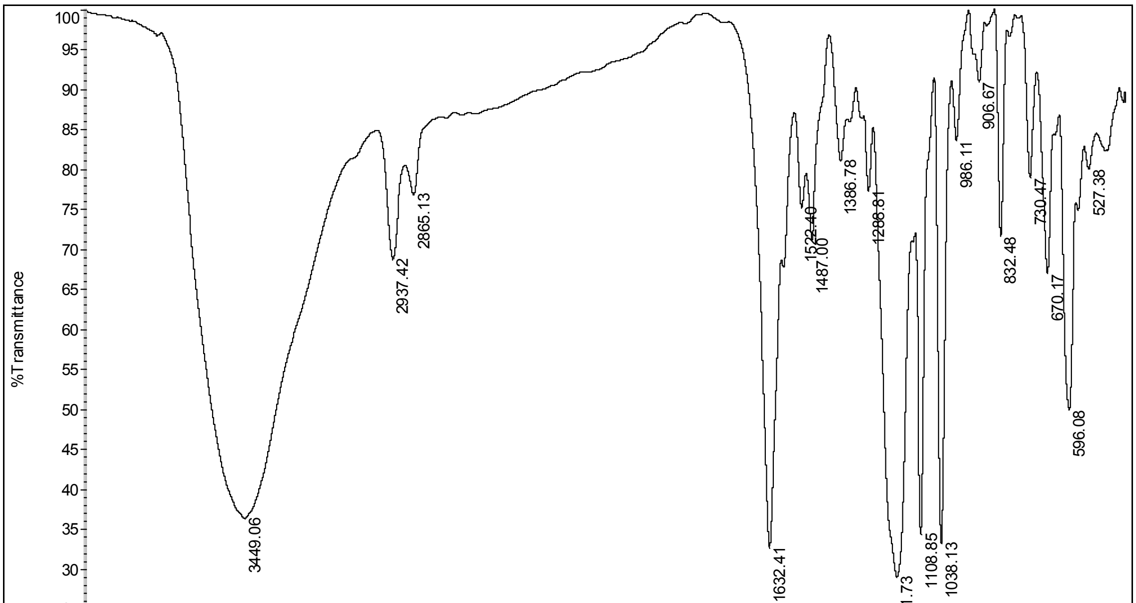


Figure 3.44: IR Spectra of **(IV)**

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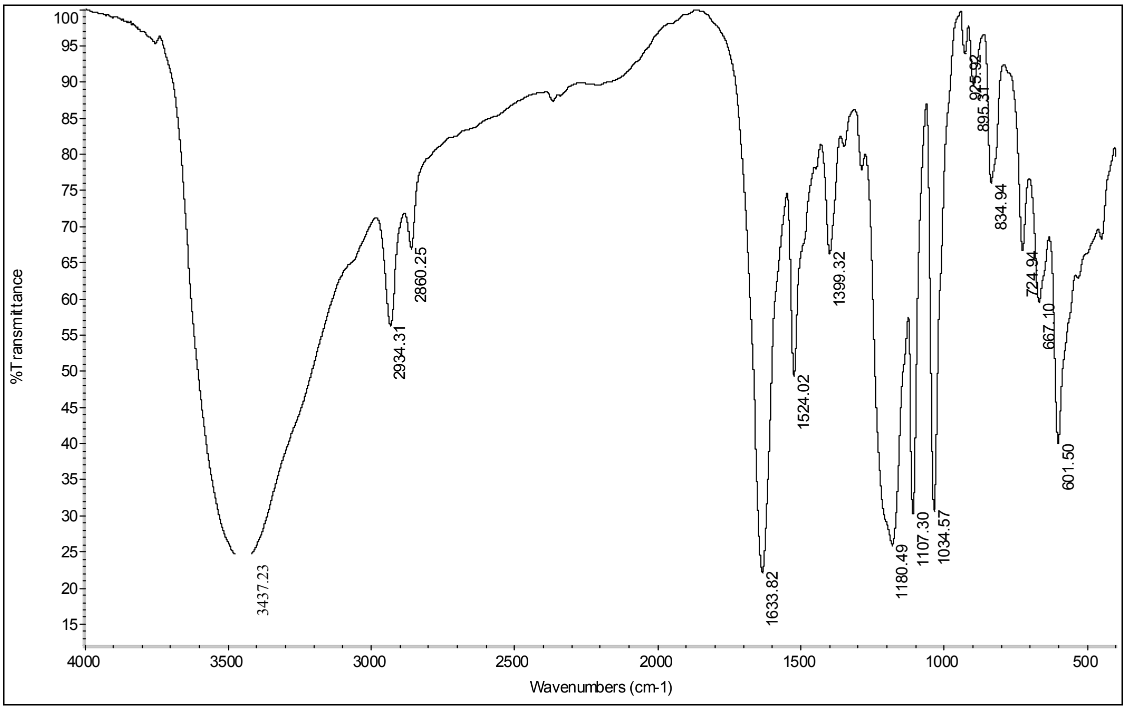


Figure 3.45: IR Spectra of **(V)**

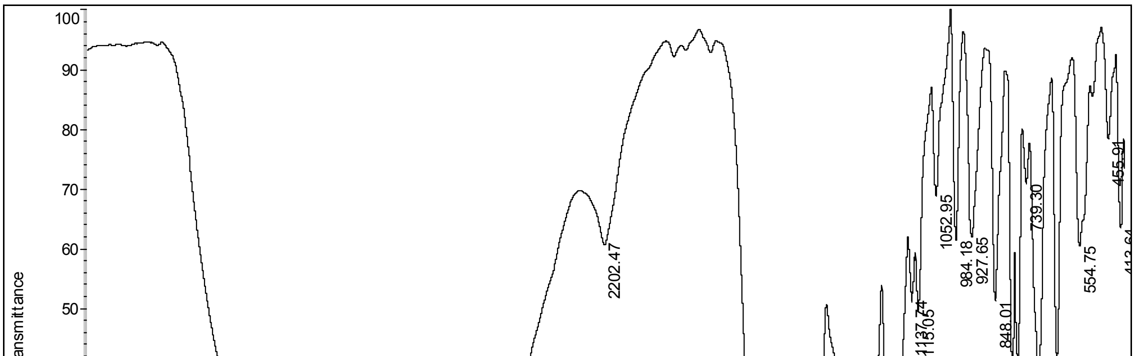


Figure 3.46: IR Spectra of **(VI)**

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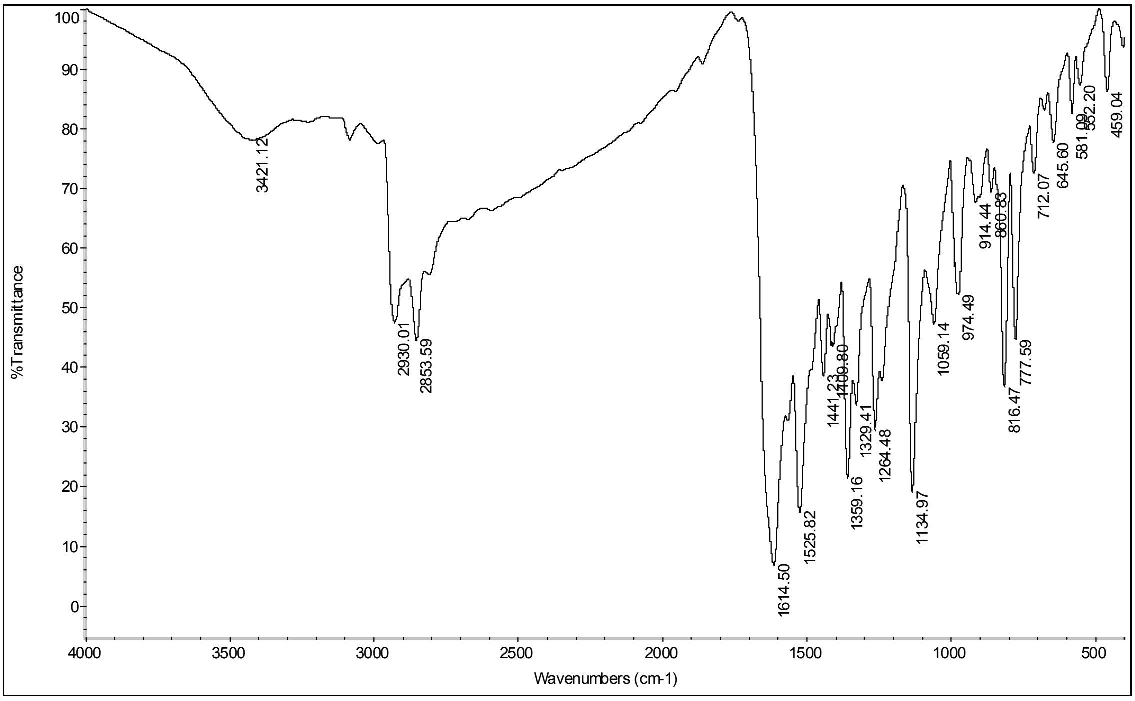


Figure 3.47: IR Spectra of **(VII)**

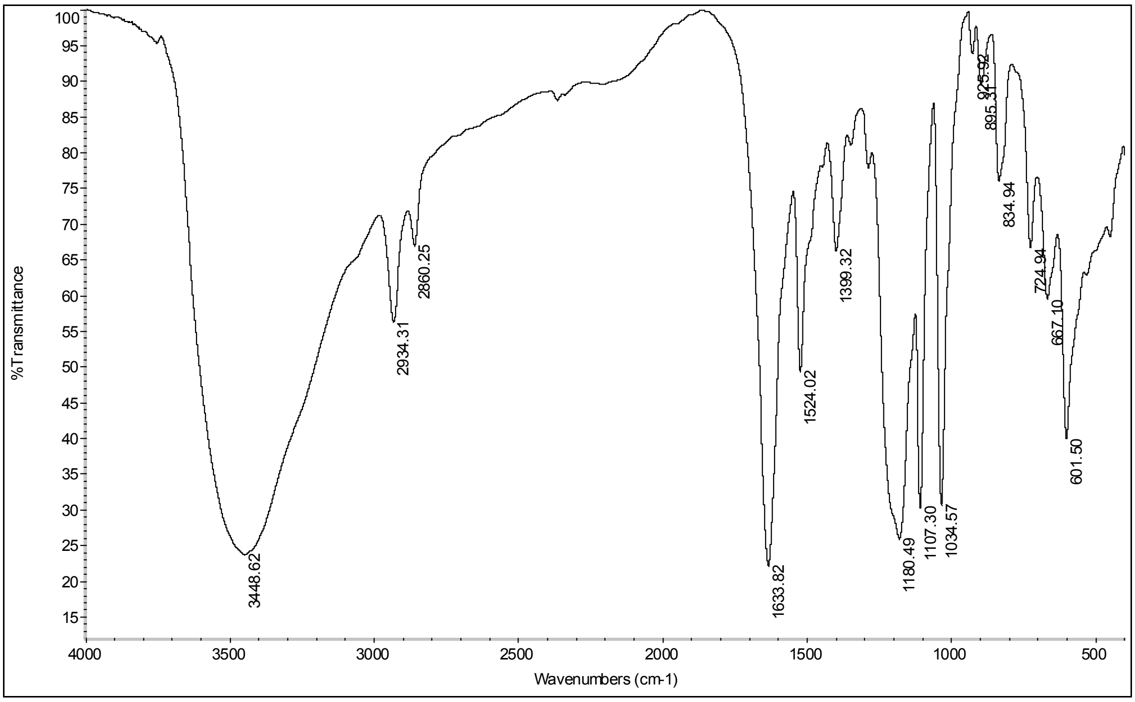


Figure 3.48: IR Spectra of **(VIII)**

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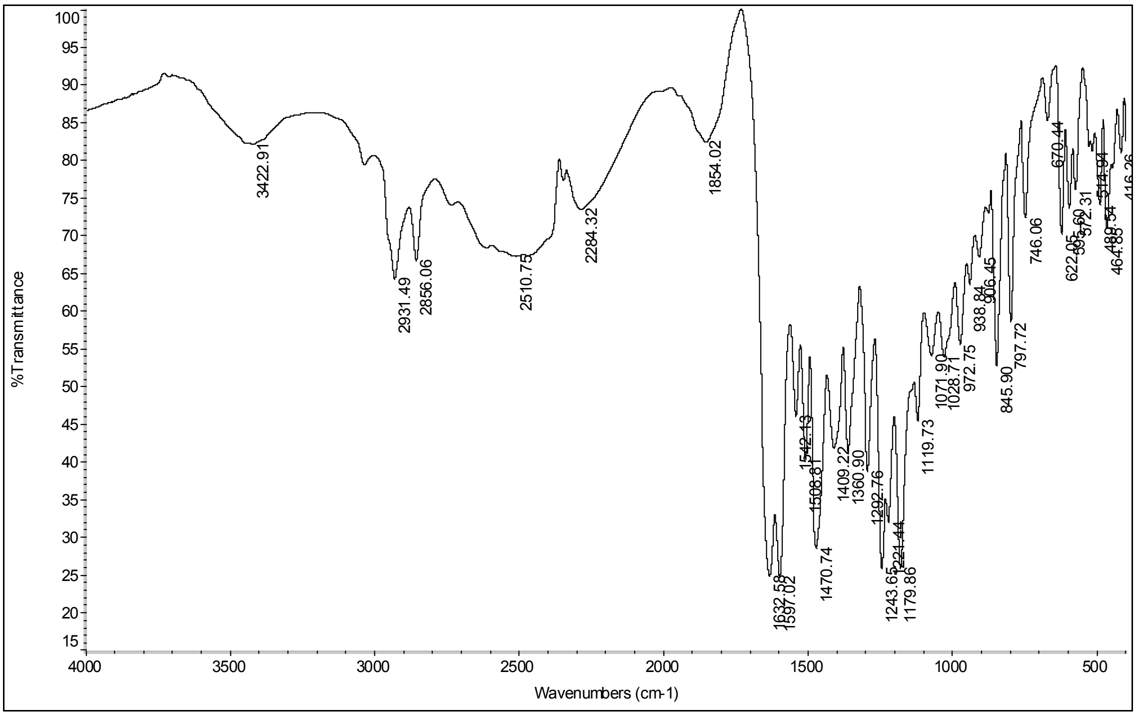


Figure 3.49: IR Spectra of **(IX)**

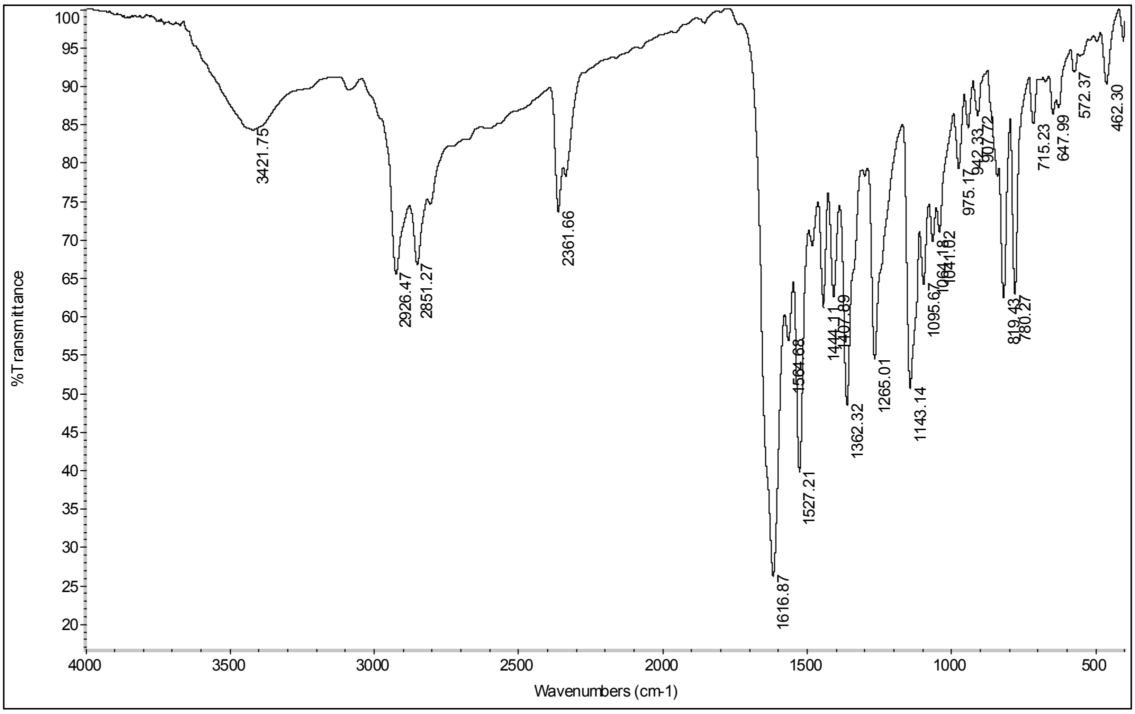


Figure 3.50: IR Spectra of **(X)**

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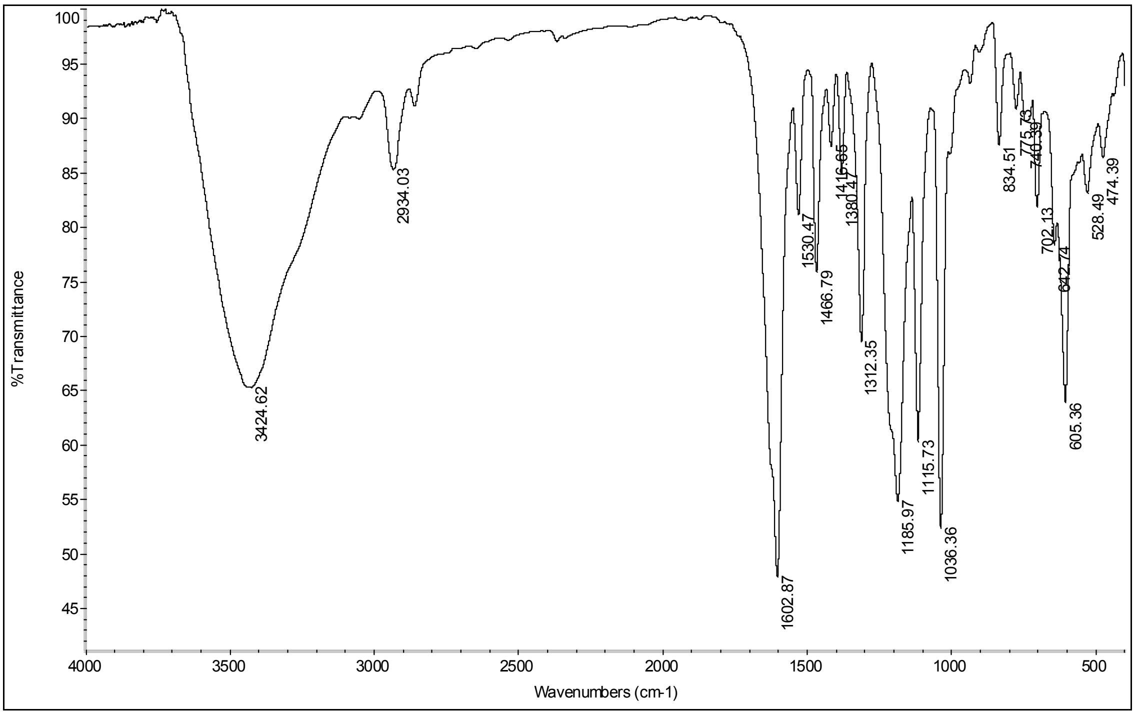


Figure 3.51: IR Spectra of **(XI)**

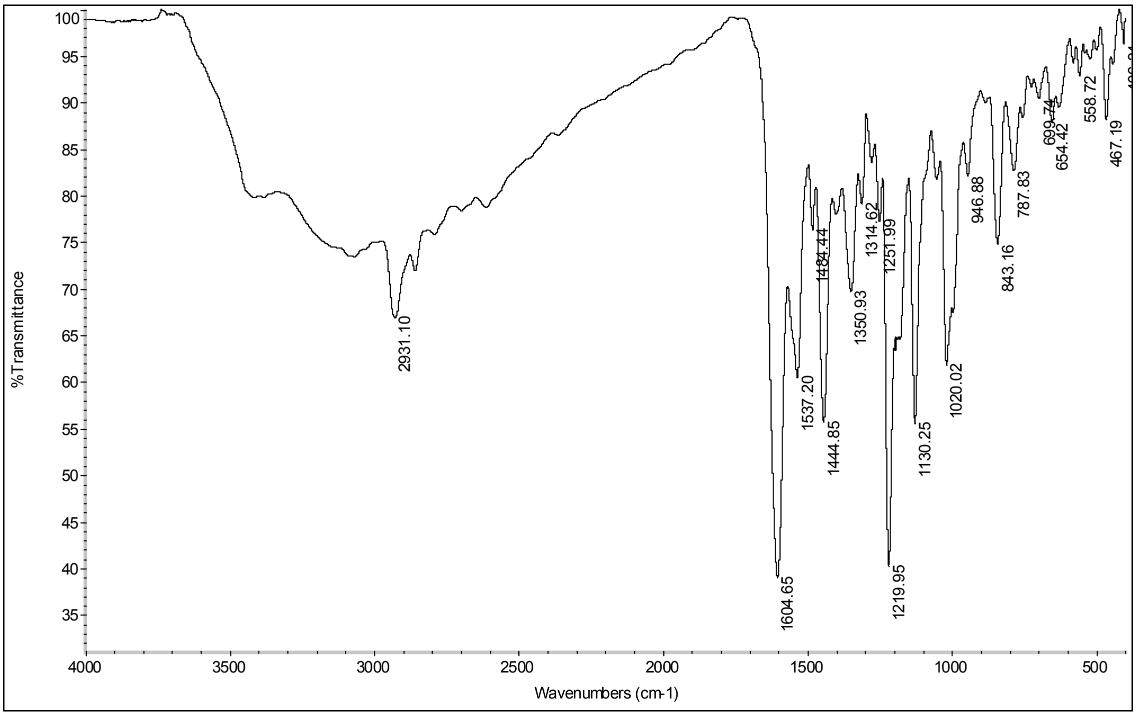


Figure 3.52: IR Spectra of **(XII)**

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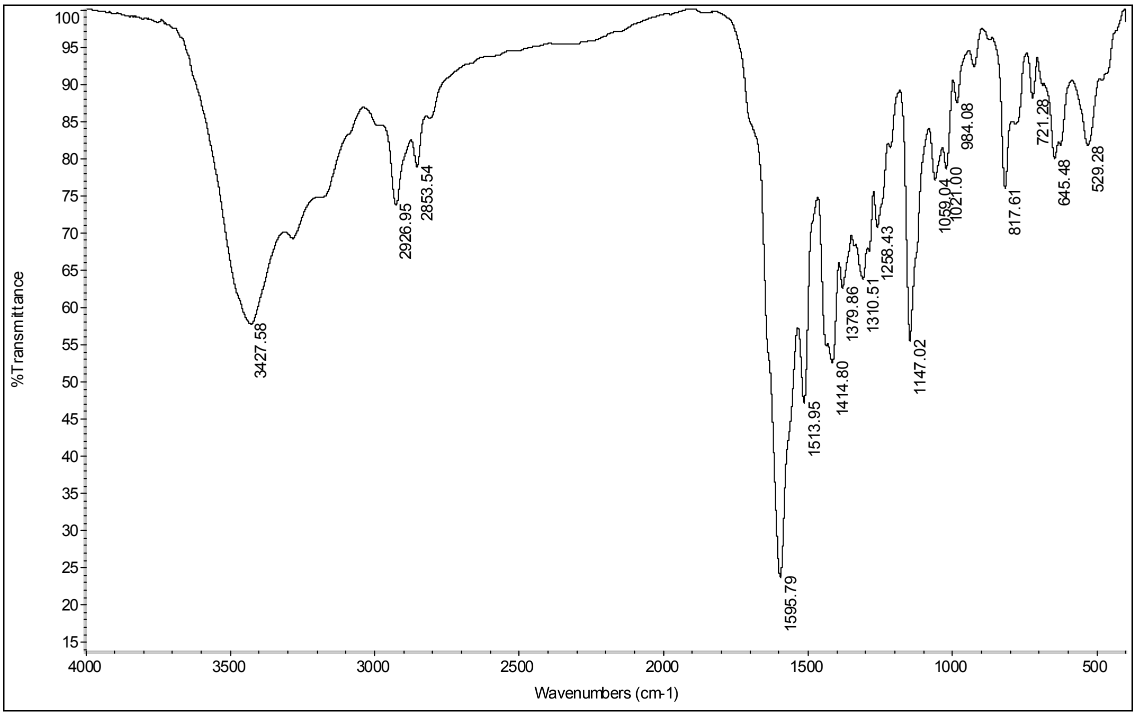


Figure 3.53: IR Spectra of **(XIV)**

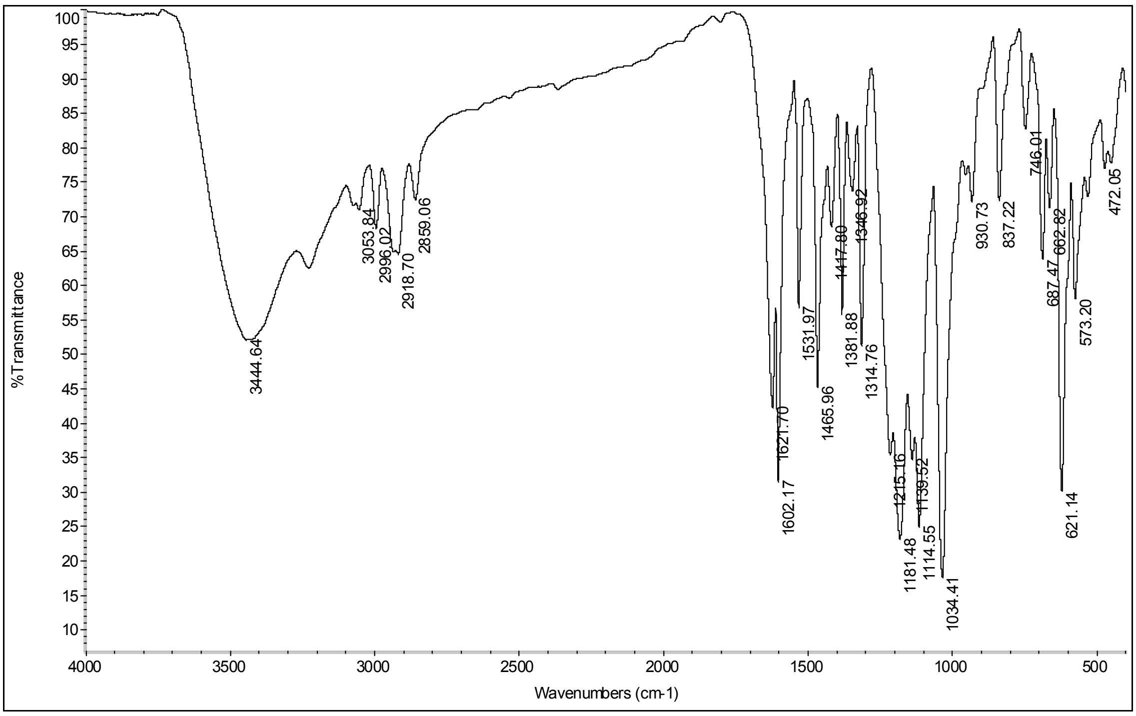


Figure 3.54: IR Spectra of **(XV)**

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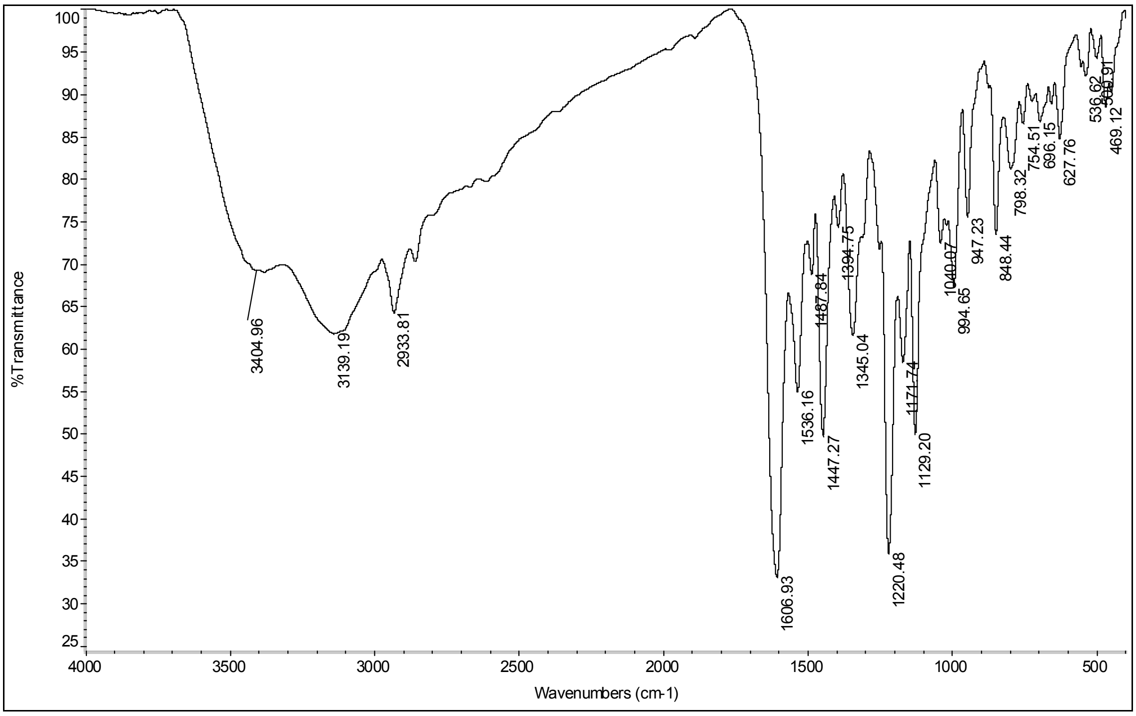


Figure 3.55: IR Spectra of **(XVI)**

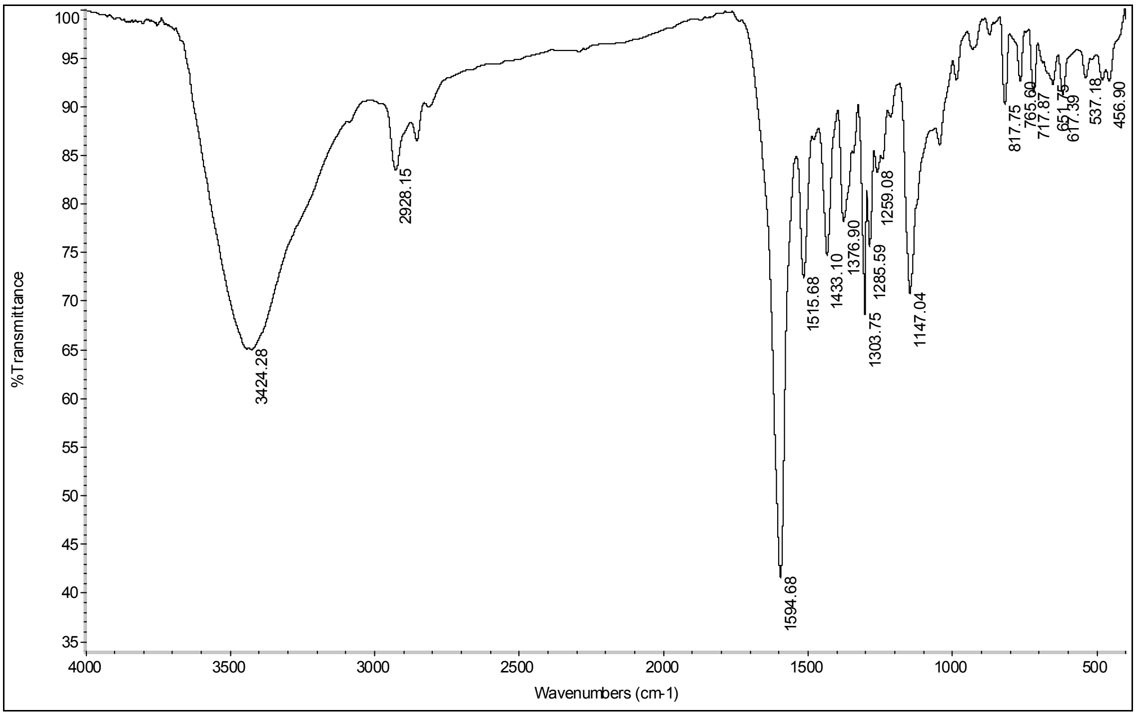


Figure 3.56: IR Spectra of **(XVII)**

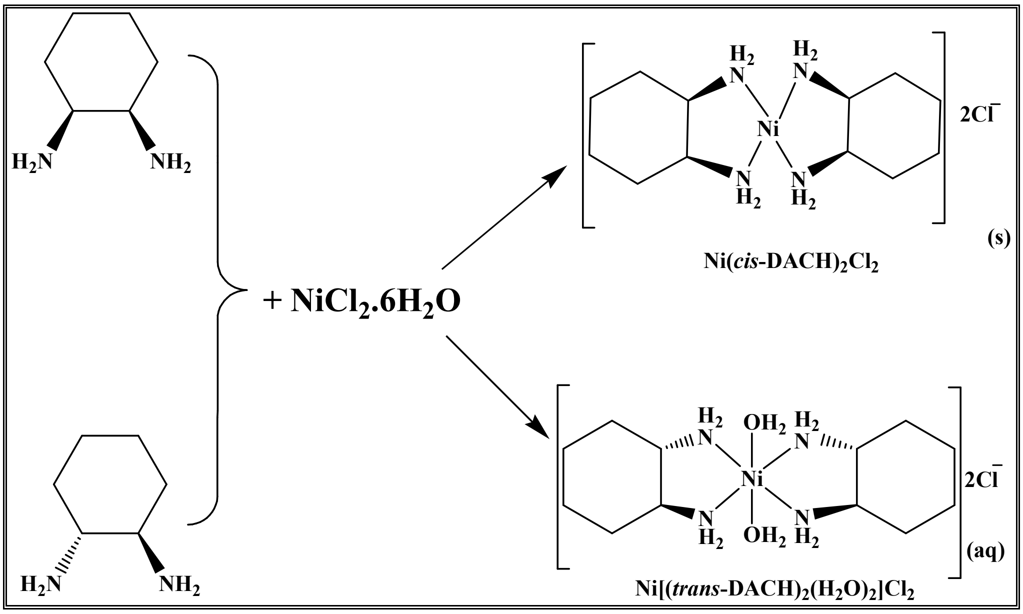
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4. DISCUSSION

4.1 Preparation of the Starting Materials:

4.1.1 Separation of *cis*-1,2-Diaminocyclohexane (*cis*-DACH) and *trans*-1,2-Diaminocyclohexane (*trans*-DACH) from a Mixture of *cis*- and *trans*-1,2-Diaminocyclohexane Via Selective Formation of Nickel (II) Complex.

The two geometrical isomers, *cis*-1,2-diaminocylohexane and *trans*-1,2-diaminocylohexane were separated from their mixture by the selective formation of nickel**(II)** complexes, as shown in scheme 4.1:

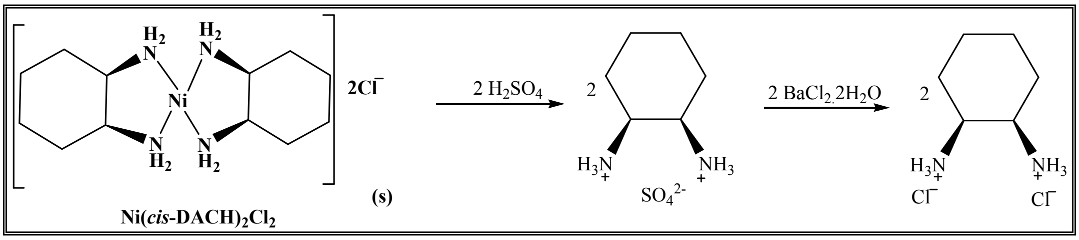


Scheme 4.1: Separation of 1,2-diaminocylohexane mixture into *cis*- and *trans*- isomers**.**

4.1.2 Preparation of *cis*-1,2-Diaminocyclohexane Dihydrochloride (*cis*-DACH.2HCl):

This compound was prepared following a literature procedure (Saito and Kidani, 1976) with some modifications. The decomposition of Ni(*cis*-DACH)$_2$Cl$_2$ using H_2SO_4 led to the formation of *cis*-DACH.H_2SO_4, followed by the conversion of the latter compound to *cis*-DACH.2HCl upon addition of $BaCl_2.2H_2O$, as shown in scheme 4.2.

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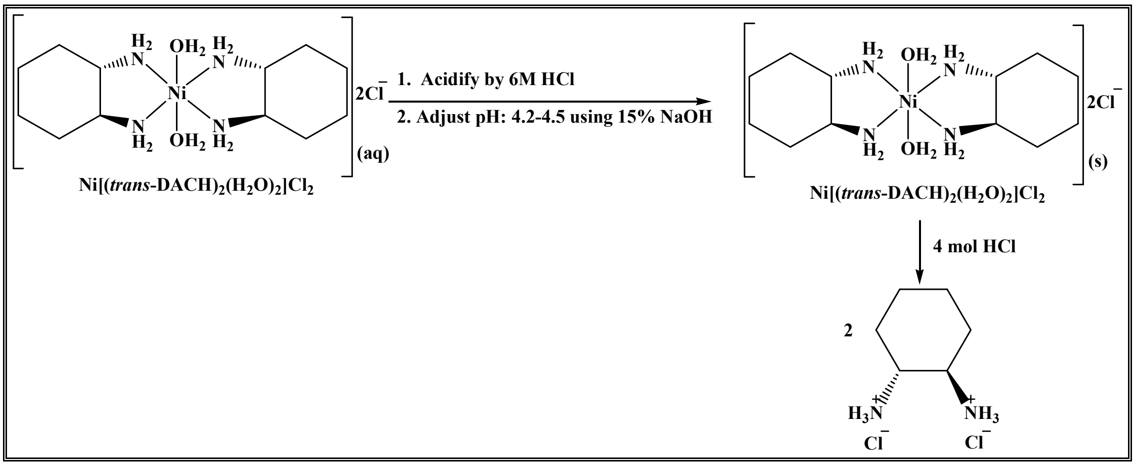


Scheme 4.2: Preparation of *cis*-DACH.2HCl.

cis-DACH.2HCl was collected as a white powder and characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum (Figure 3.39) of *cis*-DACH.2HCl shows a strong band at 3446 cm^{-1} was assigned to the $\upsilon_{N\text{-}H}$. The ^{1}H-NMR (300 MHz, D_2O) spectrum for *cis*-DACH.2HCl (Table 3.4; Figure 3.1) shows three signals resonating at δ = 3.59 (2H, t, ^{3}J = 4.46, -H^a), 1.69 (4H, m, -H^b) and δ 1.38 (4H, m, -H^c). The ^{13}C-NMR (75 MHz, D_2O) spectrum (Table 3.5; Figure 3.2) shows six signals resonating at δ = 49.9 ppm and 52.2 ppm for (C-1 and C-2), 25.7 ppm and 29.2 ppm for (C-3 and C-4), 20.2 ppm and 22.7 ppm for (C-5 and C-6).

4.1.3 Preparation of *trans*-1,2-Diaminocyclohexane Dihydrochloride (*trans*-DACH.2HCl):

This compound was prepared following literature procedure (Saito and Kidani, 1976) with some modifications. *trans*-DACH.2HCl was prepared by the collection of solid Ni[(*trans*-DACH)$_2$(H_2O)$_2$]Cl_2 complex followed by the decomposition of the complex using 6.0 M HCl, as shown in scheme. 4.3.



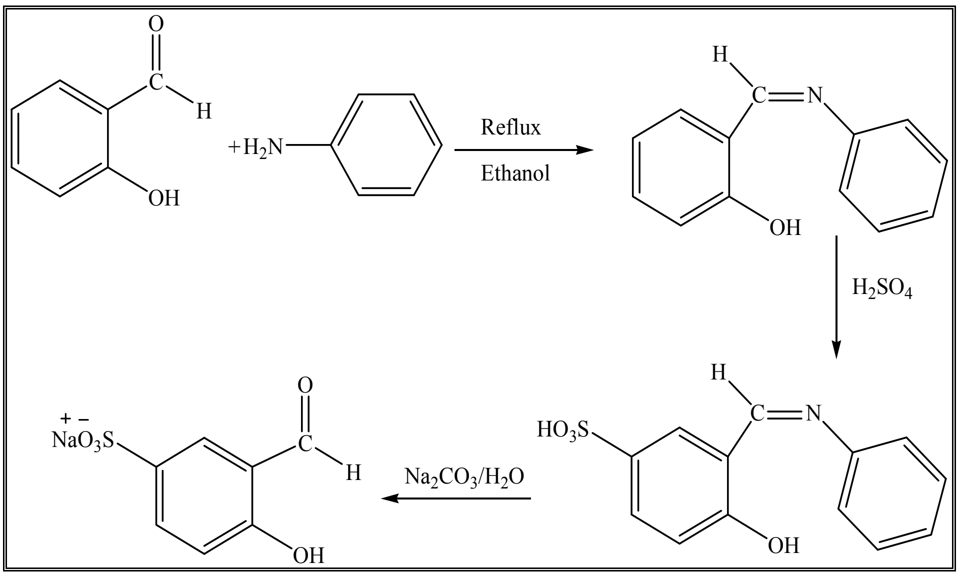
Scheme 4.3: Preparation of *trans*-DACH.2HCl.

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trans-DACH.2HCl was collected as a white powder and characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of *trans*-DACH.2HCl (Figure 3.40) shows a strong band at 3440 cm^{-1} was assigned to the υ_{N-H} which is relatively the same as *trans*-DACH.2HCl. The ^{1}H-NMR (300 MHz, D_2O) spectrum for *trans*-DACH.2HCl (Table 3.4; Figure 3.3) shows five different signals which resonating at δ = 3.22 (2H, m, -H^{a}), 2.00 (2H, m, -H^{b}), 1.69 (2H, m, -H^{b}), 1.35 (2H, m,-H^{c}) and 1.20 (2H, m, -H^{c}), so we can distinguish between *cis*- and *trans*- isomers using ^{1}H-NMR. The ^{13}C-NMR (75 MHz, D_2O) spectrum (Table 3.5; Figure 3.4) shows only three different signals resonating at δ = 52.2 ppm for (C-1 and C-2), 29.2 ppm for (C-3 and C-4), 22.7 ppm for (C-5 and C-6), which is different from the *cis*-DACH.

4.1.4 Preparation of (I):

The title compound was prepared in three steps as illustrated in scheme (4.4). The first step involves a protection of the aldehyde group via condensation with aniline to form N-phenylsalicylaldimine (Khera, et al., 1983). Sulfonation of the product using concentrated sulfuric acid produces N-phenylsalicylaldimine-5-sulfonic acid (Berry, et al., 1982). Hydrolysis of the product affords compound **(I)**(Botsivali, et al., 1985).



Scheme 4.4: Preparation of **(I)**

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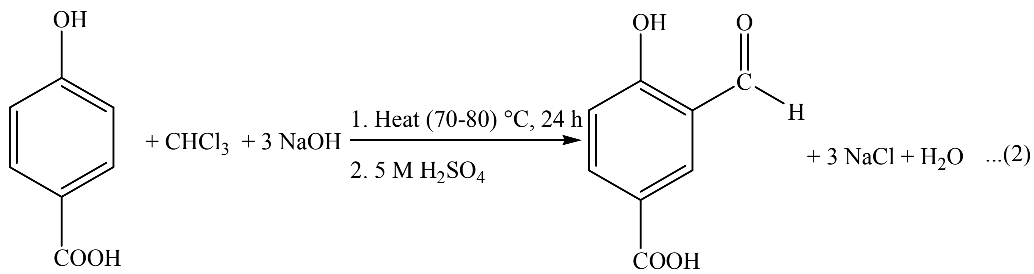
Compound **(I)** was collected as a yellow crystals and characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(I)** (Figure 3.41) shows a strong band at 1661 cm^{-1} was assigned to $\upsilon_{C=O}$ of the aldehyde group. The broad band at 3432 cm^{-1} assigned to the υ_{O-H}, which is broad due to hydrogen bonding with the adjacent aldehyde group. Strong vibration bands at 1037, 1104, and 1191 cm^{-1} were assigned to the sulfonyl group.

The ^{1}H-NMR (300 MHz, DMSO-d$_6$) spectrum for **(I)** (Table 3.6; Figure 3.5) shows signals at δ = 10.23(H, s, -C***H***O) and 10.88 (H, s, broad, -O***H***). The aromatic protons show signals at δ = 6.90 (H, d, ^{3}J = 8.5, -H^{c}), 7.68 (H, dd, ^{3}J = 8.5, ^{4}J = 2.3, -H^{d}) and 7.86 (H, d, ^{4}J = 2.3, -H^{e}).

The ^{13}C-NMR (75 MHz, DMSO-d$_6$) spectrum for **(I)** (Table 3.7; Figure 3.6) shows signals at δ = 121.5 ppm for (C-1), 161.3 ppm for (C-2), 117.1 ppm for (C-3), 134.2 ppm for (C-4), 140.4 ppm for (C-5), 126.6 ppm for (C-6) and 191.8 ppm for the aldehyde carbon(-***C***HO, C-7).

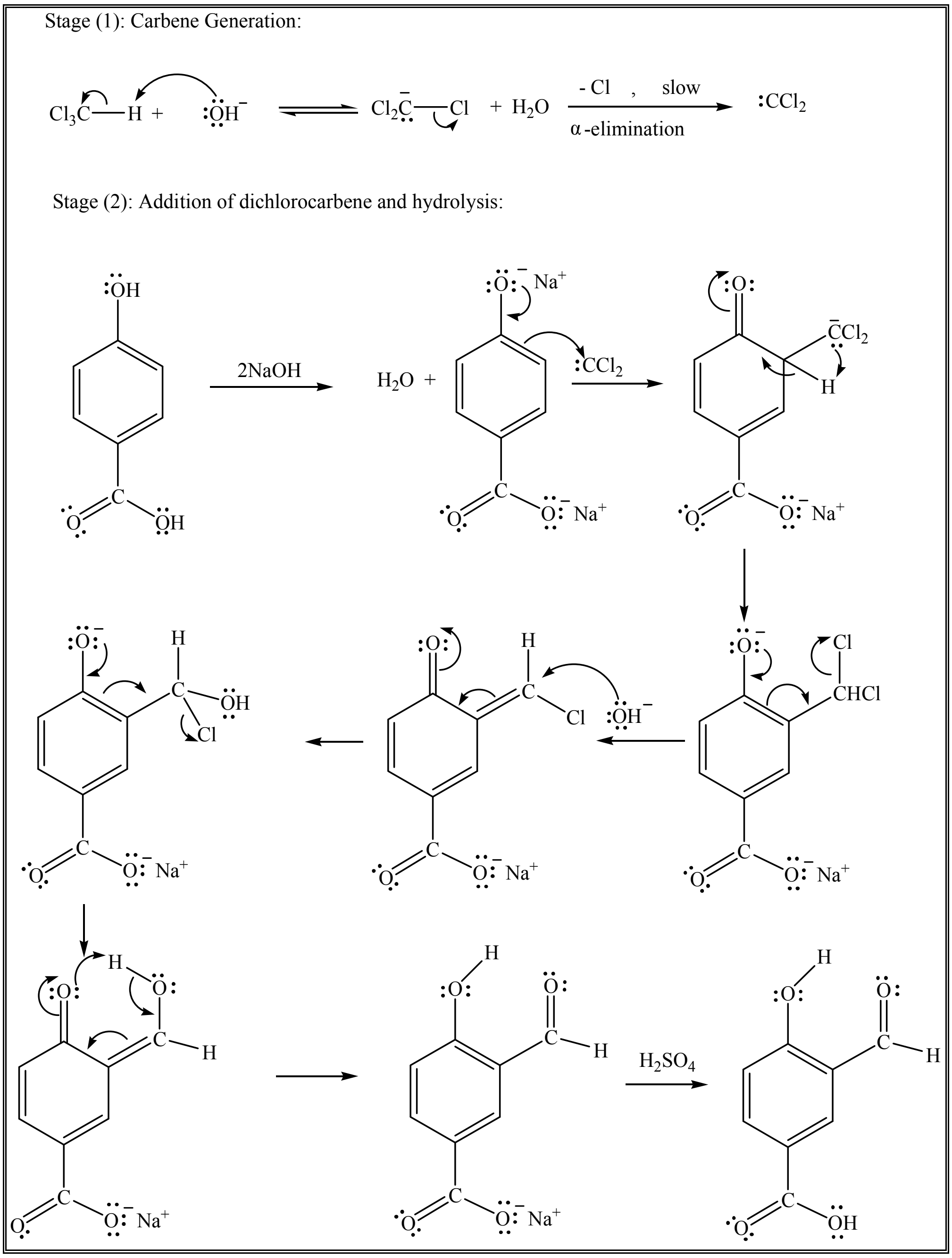
4.1.5 Preparation of (II):

The title compound was prepared, by Reimer-Tiemann reaction, following a literature procedure (Wynberg, 1954) with some modifications, as shown in eq. (2).



The expected reaction mechanism for Reimer-Tiemann reaction is summarized in scheme 4.5 (Li, 2003):

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Scheme 4.5: Mechanism of Reimer-Tiemann reaction to produce **(II)**.

Compound **(II)** was collected as off-white crystals and characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(II)** (Figure 3.42) shows a strong broad band at 1668 cm^{-1} was assigned to $\upsilon_{C=O}$ of the aldehyde and carboxyl acid. The broad band at 3442 cm^{-1} was assigned to the $\upsilon_{O\text{-}H}$, which is broad due to hydrogen

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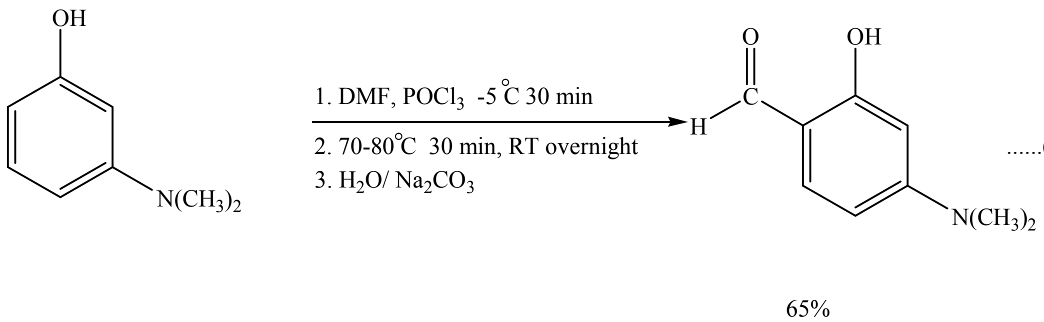
bonding with the adjacent aldehyde group. The broad band at 2590 cm^{-1} was assigned to the $\upsilon_{O\text{-}H}$ of the carbonyl group.

The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(II)** (Table 3.6; Figure 3.7) shows signals at δ = 10.26 (H, s, -C***H***O), 11.69 (H, s, broad, -O***H***) and 12.64 (H, s, broad, carboxyl (-O***H***)). The aromatic protons show signals at δ = 7.04 (H, d, ^{3}J = 8.7, -H^c), 8.00 (H, dd, ^{3}J = 8.7, ^{4}J = 2.2, -H^d) and 8.20 (H, d, ^{4}J = 2.2, -H^e).

The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(II)** (Table 3.7; Figure 3.8) shows signals at δ = 122.5 ppm for (C-1), 164.6 ppm for (C-2), 118.0 ppm for (C-3), 137.3 ppm for (C-4), 122.4 ppm for (C-5), 131.2 ppm for (C-6), 191.1 ppm for the aldehyde carbon(-***C***HO, C-7) and 166.9 ppm for the carbonyl carbon of the carboxyl group (-***C***=O, C-8).

4.1.6 Preparation of (III):

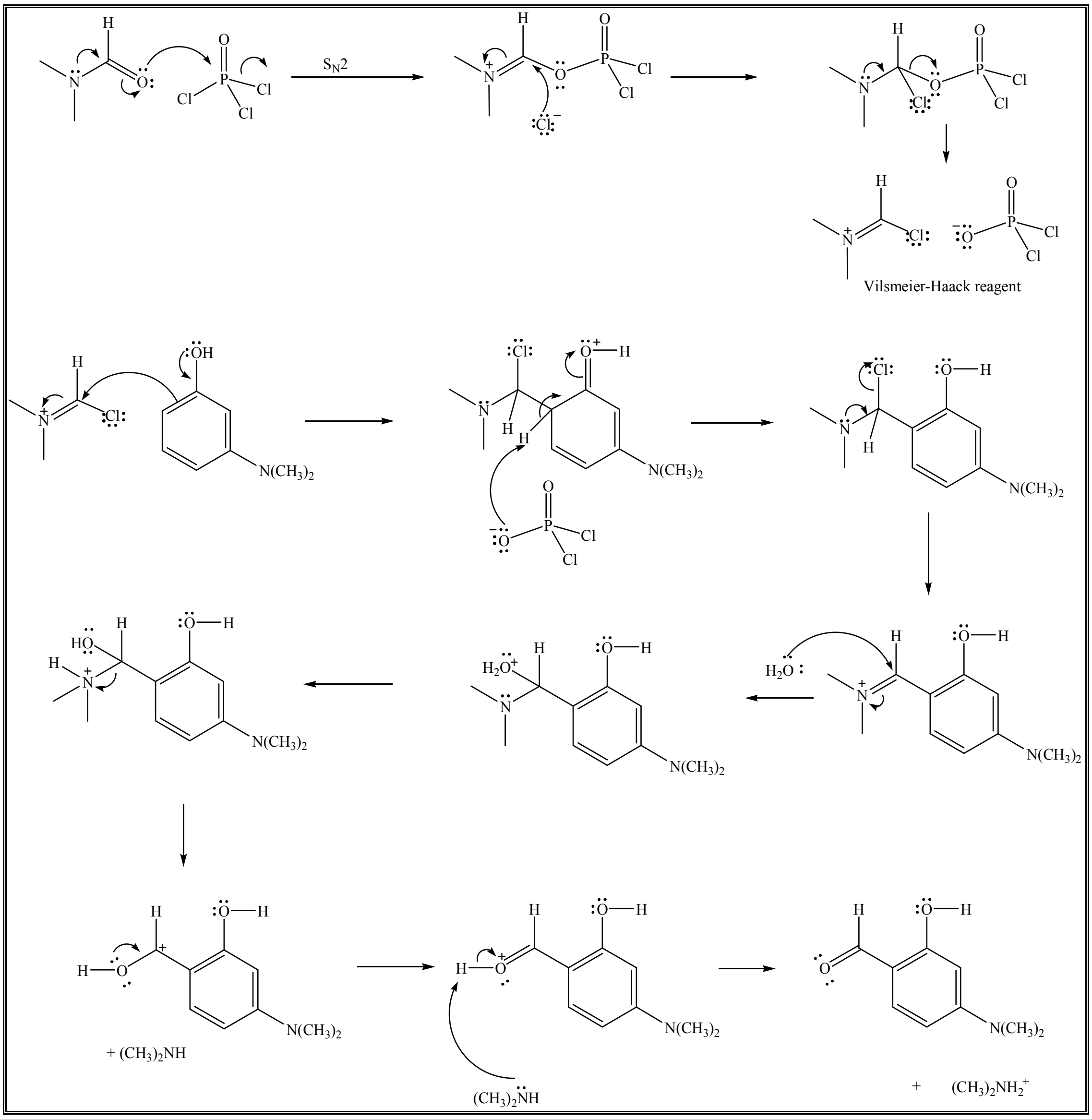
The title compound was prepared, by Vilsmeier-Haack reaction, following literature procedure with some modifications (Flašík, et al., 2009), as shown in eq. (3)



......(3)

The expected reaction mechanism for Vilsmeier-Haack reaction is summarized in scheme 4.6 (Li, 2003):

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Scheme 4.6: Mechanism of Vilsmeier-Haack reaction to produce **(III)**

Compound **(III)** was collected as off-white powder and characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(III)** (Figure 3.43) shows a strong band at 1646 cm^{-1} was assigned to $\upsilon_{C=O}$ of the aldehyde. The broad band at 3457 cm^{-1} was assigned to the $\upsilon_{O\text{-}H}$, which is broad due to hydrogen bonding with the adjacent aldehyde group.

The ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum for **(III)** (Table 3.8; Figure 3.9) shows signals at δ = 9.50 (H, s, -C***H***O), 11.58 (H, s, -O***H***) and 3.04 (6H, s, -N(C$\boldsymbol{H_3}$)$_2$).

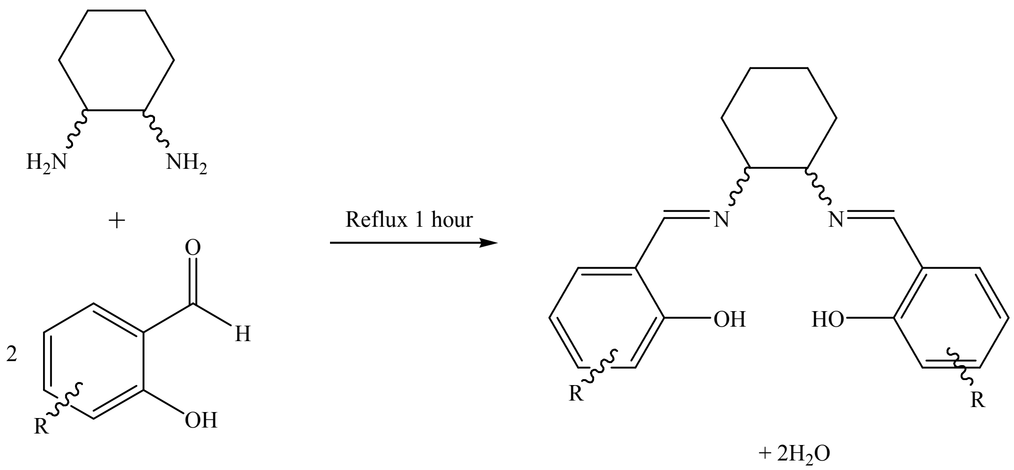
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The aromatic protons show signals at δ = 6.06 (H, d, ^{4}J = 2.3, -H^{c}), 6.26 (H, dd, ^{3}J = 8.9, ^{4}J = 2.3, -H^{e}) and 7.26 (H, d, ^{3}J = 8.9, -H^{f}).

The ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum for **(III)** (Table 3.9; Figure 3.10) shows signals at δ = 111.7 ppm for (C-1), 164.3 ppm for (C-2), 97.3 ppm for (C-3), 156.2 ppm for (C-4), 104.6 ppm for (C-5), 135.2 ppm for (C-6), 192.4 ppm for the aldehyde carbon(-***C***HO, C-7) and 40.1 for methyl carbons(-***C***H_3, C-8).

4.2 Preparation of Schiff Bases Ligands:

All ligands were prepared by condensation of *cis*- or *trans*-1,2-diaminocyclohexane with suitable substituted salicyaldehyde in 1:2 molar ratio, eq. (4):



.... (4)

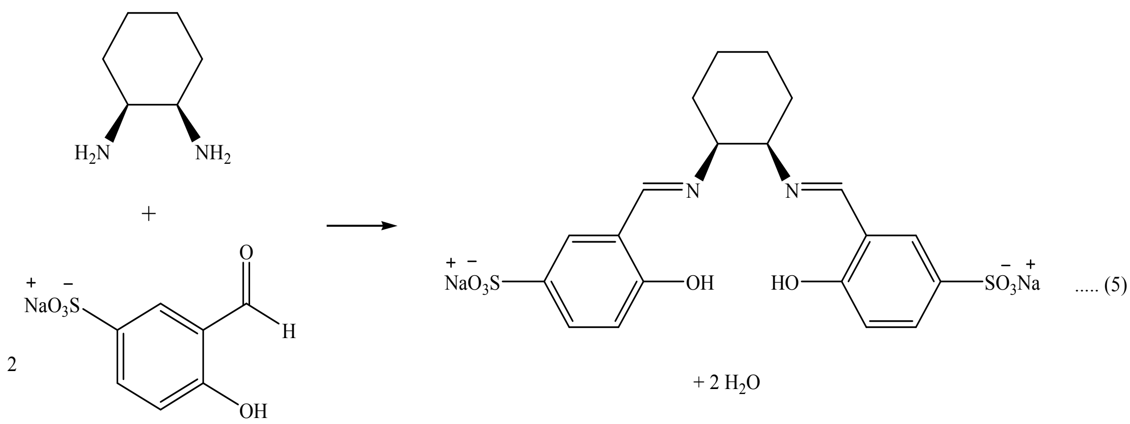
where R:SO_3Na, OH, COOH and $N(CH_3)_2$

4.2.1 Schiff Bases Derived from *cis*-1,2-Diaminocyclohexane (*cis*-DACH):

4.2.1.a Preparation of (IV):

Compound **(I)** was condensed with *cis*-1,2-diaminocyclohexane in 2:1 molar ratio to produce **(IV)**, as shown below:

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Compound **(IV)** was collected as yellow powder; its melting point is greater than 360.0 °C. Compound **(IV)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(IV)** (Figure 3.44) shows a strong band at 1632 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. The broad band at 3454 cm^{-1} was assigned to the $\upsilon_{O\text{-}H}$, which is broad due to hydrogen bonding with the adjacent azomethine group. Strong vibration bands at 1039, 1109, and 1191 cm^{-1} were assigned to the sulfonyl group.

The ^{1}H-NMR (300 MHz, DMSO-d$_6$) spectrum for **(IV)** (Table 3.10; Figure 3.11) shows the cyclohexane protons at δ = 3.67 (2H, m, -H^a), 1.74 (6H, m, -H^b + H^c) and 1.71 (2H, m, -H^b + H^c). In addition, other protons resonate at δ = 8.60 (2H, s, -C***H***=N) and 13.90 (2H, s, broad, -O***H***). The aromatic protons show signals at δ = 7.65 (2H, d, ^{4}J = 2.1, -H^e), 7.5 (2H, dd, ^{3}J = 8.6, ^{4}J = 2.1, -H^f) and 6.75 (2H, d, ^{3}J = 8.6, -H^g).

The ^{13}C-NMR (75 MHz, DMSO-d$_6$) spectrum for **(IV)** (Table 3.11; Figure 3.12a) shows signals at δ = 139.3 ppm for (C-1), 130.4 ppm for (C-2), 117.6 ppm for (C-3), 161.8 ppm for (C-4), 116.4 ppm for (C-5), 129.5 ppm for (C-6), 165.8 ppm for (C-7), 68.2 ppm for (C-8), 30.9 ppm for (C-9) and 22.4 ppm for (C-10).

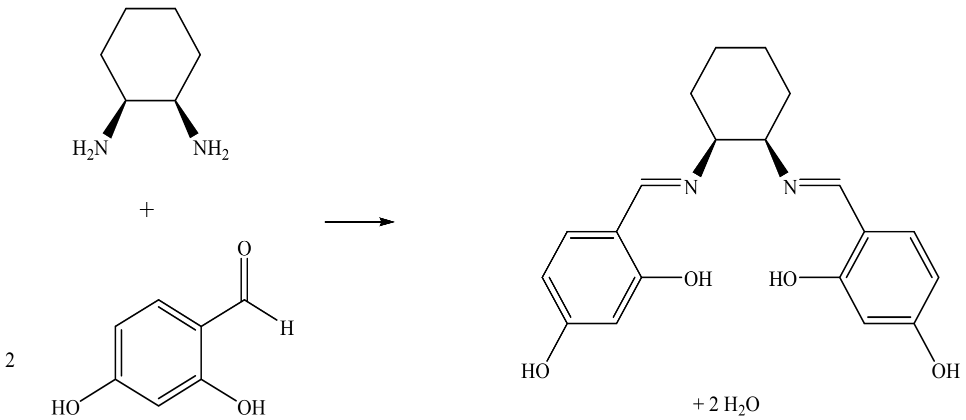
The above NMR spectral data were confirmed using the DEPT-135 experiment (Figure 3.12b) which shows the disappearance of the quaternary carbons at δ = 139.3

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ppm (C-1), 117.6 ppm (C-3) and 161.8 ppm (C-4), and inversion of $-CH_2-$ carbons at δ = 30.9 ppm (C-9) and 22.4 ppm (C-10).

4.2.1.b Preparation of (V):

The title compound was prepared following literature procedure with some modifications (Aranha et al., 2007). DHBA was condensed with *cis*-1,2-diaminocyclohexane in 2:1 molar ratio to produce Compound **(V)**.



..... (6)

Compound **(V)** was collected as orange powder; its melting point is 260.0 - 262.0 °C. Compound **(V)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(V)** (Figure 3.45) shows a strong band at 1634 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. The broad band at 3437 cm^{-1} was assigned to the $\upsilon_{O\text{-}H}$, which is broad due to hydrogen bonding with the adjacent azomethine group.

The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(V)** (Table 3.12; Figure 3.13) shows the cyclohexane protons at δ = 3.54 (2H, m, $-H^a$), 1.69 (6H, m, $-H^b + H^c$) and 1.48 (2H, m, $-H^b + H^c$). In addition, other protons resonate at δ = 8.32 (2H, s, -C***H***=N), 9.87 (2H, s, -O***H*** (H^g)) and 13.97 (2H, s, broad, -O***H*** (H^i)). The aromatic protons show signals at δ = 7.13 (2H, d, ^{3}J = 8.5, $-H^e$), 6.22 (2H, dd, ^{3}J = 8.5, ^{4}J = 2.3, $-H^f$) and 6.09 (2H, d, ^{4}J = 2.3, $-H^h$).

The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(V)** (Table 3.13; Figure 3.14a) shows signals at δ = 162.2 ppm for (C-1), 103.0 ppm for (C-2), 165.2 ppm for (C-3),

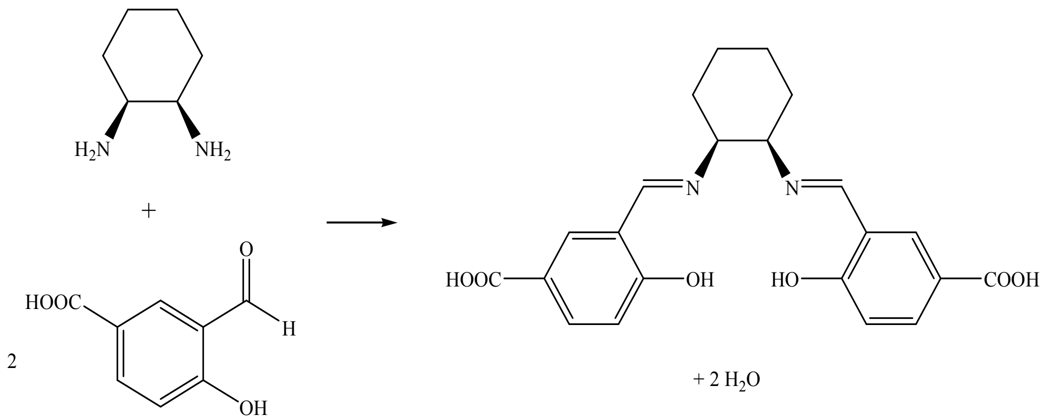
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111.9 ppm for (C-4), 133.9 ppm for (C-5), 107.3 ppm for (C-6), 164.4 ppm for (C-7), 67.5 ppm for (C-8), 30.9 ppm for (C-9) and 22.4 ppm for (C-10).

The above NMR spectral data were confirmed using the DEPT-135 experiment (Figure 3.14b) which shows the disappearance of the quaternary carbons at δ: 162.2 ppm (C-1), 165.2 ppm (C-3) and 111.9 ppm (C-4), and inversion of -CH_2- carbons resonate at δ = 30.9 ppm (C-9) and 22.4 ppm (C-10).

4.2.1.c Preparation of (VI):

Compound **(II)** was condensed with *cis*-1,2-diaminocyclohexane in 2:1 molar ratio to produce **(VI)**.



..... (7)

Compound **(VI)** was collected as orange powder; with a melting point of 285.0 - 287.0 °C. Compound **(VI)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(VI)** (Figure 3.46) shows a strong band at 1633 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. The broad band at 3443 cm^{-1} was assigned to the $\upsilon_{O\text{-}H}$, which is broad due to hydrogen bonding with the adjacent azomethine group. The broad band at 2700 cm^{-1} was assigned to the other $\upsilon_{O\text{-}H}$ of the carboxyl group which is broad due to hydrogen bonding with the adjacent carbonyl group.

The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(VI)** (Table 3.14; Figure 3.15) shows the cyclohexane protons at δ = 3.75 (2H, m, -H^a), 1.87 (6H, m, -H^b + H^c) and 1.55 (2H, m, -H^b + H^c). In addition, other protons resonate at δ = 8.68 (2H, s, -

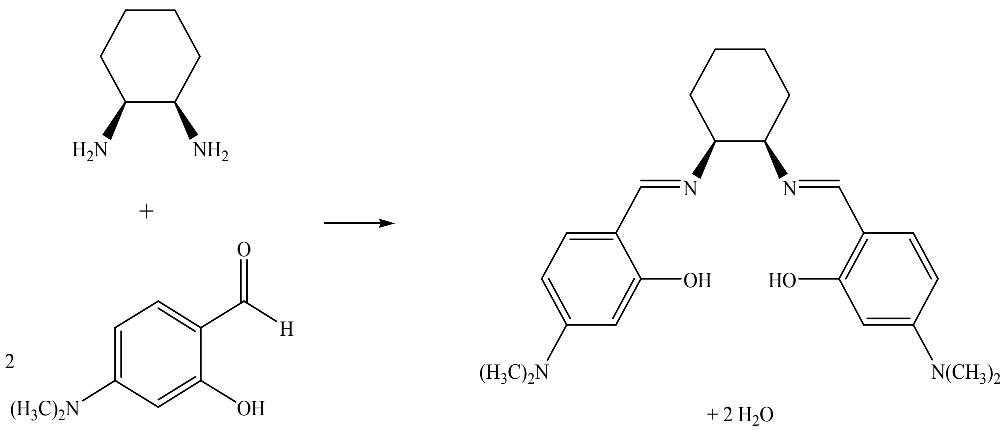
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C***H***=N), 14.50 (2H, s, broad, -O***H***). The aromatic protons show signals at δ = 8.02 (2H, s, -H[e]), 7.81 (2H, d, ^{3}J = 8.8, -H[g]) and 6.82 (2H, d, ^{3}J = 8.8, -H[h]). Neither the hydrogen of carboxylic acid nor long range coupling appeared.

The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(VI)** (Table 3.15; Figure 3.16) shows signals at δ = 134.7 ppm for (C-1), 166.1 ppm for (C-4), 118.0 ppm for (C-5), 167.3 ppm for (C-7), 166.8 ppm for (C-8), 67.2 ppm for (C-9), 22.4 ppm for (C-11). No signals were obtained for other carbons due to the low solubility of **(VI)** in DMSO-d_6.

4.2.1.d Preparation of (VII):

Compound **(III)** was condensed with *cis*-1,2-diaminocyclohexane in 2:1 molar ratio to produce **(VII)**.



..... (8)

Cmpound **(VII)** was collected as yellow powder; its melting point is 190.0 - 192.0 °C. Compound **(VII)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(VII)** (Figure 3.47) shows a strong band at 1615 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. The broad band at 3421 cm^{-1} was assigned to the $\upsilon_{O\text{-}H}$, which is broad due to hydrogen bonding with the adjacent azomethine group.

The ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum for **(VII)** (Table 3.16; Figure 3.17) shows the cyclohexane protons at δ = 3.49 (2H, m, -H[a]), 1.82 (6H, m,-H[b] + H[c]) and 1.52 (2H, m, -H[b] + H[c]). In addition, other protons resonate at δ = 8.02 (2H, s, -C***H***=N), 13.98 (2H, s, broad, -O***H***) and 2.96 (12H, s, -N(C$\boldsymbol{H_3}$)$_2$). The aromatic protons show signals at

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δ = 6.97 (2H, d, ^3J = 8.7, -H^e), 6.14 (2H, dd, ^3J = 8.7, ^4J = 2.4, -H^f) and 6.07 (2H, d, ^4J = 2.4, -H^h).

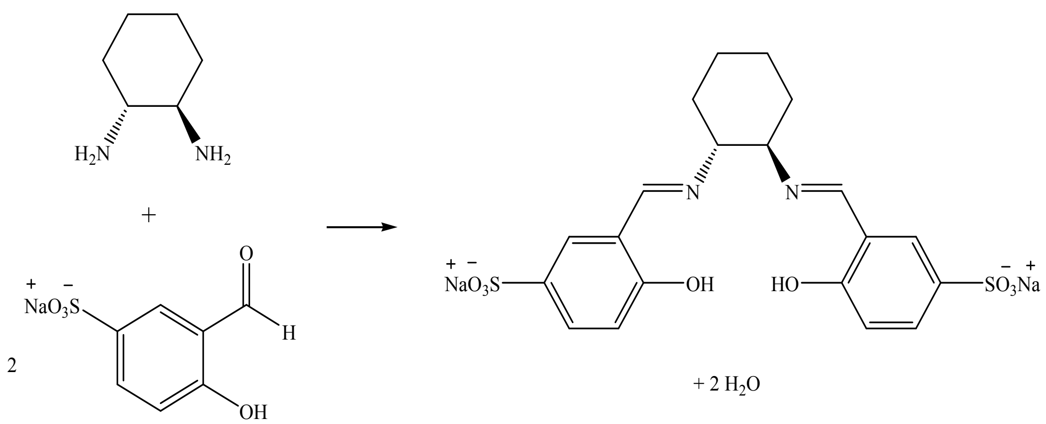
The ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum for **(VII)** (Table 3.17; Figure 3.18a) shows signals at δ = 166.1 ppm for (C-1), 109.1 ppm for (C-2), 132.8 ppm for (C-3), 103.4 ppm for (C-4), 153.9 ppm for (C-5), 99.2 ppm for (C-6), 40.1 ppm for (C-7), 162.4 ppm for (C-8), 67.3 ppm for (C-9), 30.4 ppm for (C-10) and 22.6 ppm for (C-11).

The above NMR spectral data were confirmed using the DEPT-135 experiment (Figure 3.18b) which shows the disappearance of the quaternary carbons at δ = 166.1 ppm (C-1), 109.1 ppm (C-2) and 153.9 ppm (C-5), and inversion of -CH_2- carbons resonate at δ = 30.4 ppm (C-10) and 22.6 ppm (C-11).

4.2.2 Schiff Bases Derived from *trans*-1,2-Diaminocyclohexane (*trans*-DACH):

4.2.2.a Preparation of (VIII).

The title compound was prepared following literature procedure with some modifications (Qu et al., 2010). Compound **(I)** was condensed with *trans*-1,2-diaminocyclohexane in 2:1 molar ratio to produce **(VIII)**.



..... (9)

Compound **(VIII)** was collected as yellow powder; it does not melt below 360.0 °C. Compound **(VIII)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(VIII)** (Figure 3.48) shows a strong band at 1633 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. The broad band at 3449 cm^{-1} was assigned to the υ_{O-H},

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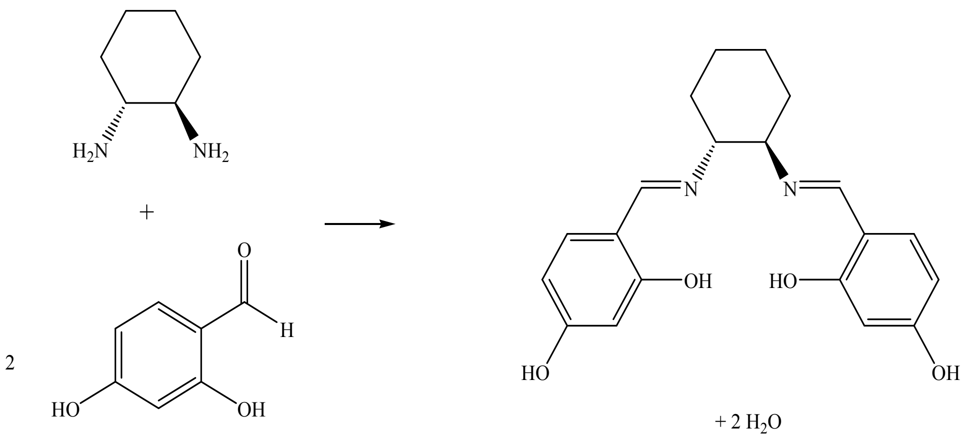
which is broad due to hydrogen bonding with the adjacent azomethine group. Strong vibration bands at 1034, 1107, and 1180 cm^{-1} were assigned to the sulfonyl group.

The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(VIII)** (Table 3.18; Figure 3.19) shows the cyclohexane protons at δ = 1.80 (4H, m, -H^b + H^c) and 1.56 (4H, m, -H^b + H^c). In addition, other protons resonate at δ = 8.53 (2H, s, -C***H***=N) and 13.51 (2H, s, broad, -O***H***). The aromatic protons show signals at δ = 7.61 (2H, d, ^4J = 2.1, -H^e), 7.47 (2H, dd, ^3J = 8.6, ^4J = 2.1, -H^f) and 6.72 (2H, d, ^3J = 8.6, -H^g). The H^a did not appear due the overlap with H_2O signal in the spectrum shown in Fig. 3.21.

The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(VIII)** (Table 3.19; Figure 3.20) shows signals at δ = 139.1 ppm for (C-1), 130.3 ppm for (C-2), 117.6 ppm for (C-3), 161.5 ppm for (C-4), 116.3 ppm for (C-5), 129.3 ppm for (C-6), 165.5 ppm for (C-7), 71.3 ppm for (C-8), 32.9 ppm for (C-9) and 24.2 ppm for (C-10).

4.2.2.b Preparation of (IX):

The title compound was prepared following literature procedure with some modifications (Aranha et al., 2007). DHBA was condensed with *trans*-1,2-diaminocyclohexane in 2:1 molar ratio to produce **(IX)**.



..... (10)

Compound **(IX)** was collected as orange powder; its melting point is 250.0 - 252.0 °C. Compound **(IX)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra.

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The IR spectrum of **(IX)** (Figure 3.49) shows a strong band at 1633 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. The broad band at 3442 cm^{-1} was assigned to the υ_{O-H}, which is broad due to hydrogen bonding with the adjacent azomethine group.

The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(IX)** (Table 3.20; Figure 2.21) shows the cyclohexane protons at δ = 3.33 (2H, m, -H^a), 1.77 (4H, m,-H^b + H^c) and 1.42 (2H, m,-H^b + H^c). In addition, other protons resonate at δ = 8.23 (2H, s, -C***H***=N), 9.55 (2H, s, -O***H*** (H^g)) and 13.62 (2H, s, broad, -O***H*** (H^i)). The aromatic protons show signals at δ = 7.05 (2H, d, ^{3}J = 8.4, -H^e), 6.18 (2H, dd, ^{3}J = 8.4, ^{4}J = 2.2, -H^f) and 6.08 (2H, d, ^{4}J = 2.2, -H^h).

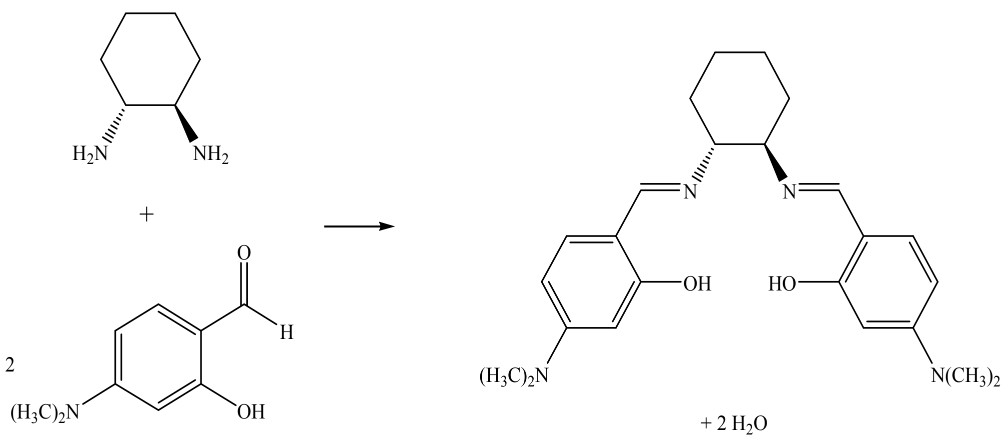
The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(IX)** (Table 3.21; Figure 3.22a) shows signals at δ = 162.0 ppm for (C-1), 102.9 ppm for (C-2), 164.6 ppm for (C-3), 111.6 ppm for (C-4), 133.7 ppm for (C-5), 107.4 ppm for (C-6), 164.3 ppm for (C-7), 71.0 ppm for (C-8), 33.2 ppm for (C-9) and 24.3 ppm for (C-10).

The above NMR spectral data were confirmed using the DEPT-135 experiment (Figure 3.22b) which shows the disappearance of the quaternary carbons at δ: 162.0 ppm (C-1), 164.6 ppm (C-3) and 111.6 ppm (C-4), and inversion of -CH_2- carbons resonate at δ = 33.2 ppm (C-9) and 24.3 ppm (C-10).

4.2.2.c Preparation of (X):

Compound **(III)** was condensed with *trans*-1,2-diaminocyclohexane in 2:1 molar ratio to produce **(X)**.

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..... (11)

Compound **(X)** was collected as orange powder; its melting point is 167.0 -169.0 °C. Compound **(X)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(X)** (Figure 3.50) shows a strong band at 1617 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. The broad band at 3421 cm^{-1} was assigned to the υ_{O-H}, which is broad due to hydrogen bonding with the adjacent azomethine group.

The ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum for **(X)** (Table 3.22; Figure 3.23) shows the cyclohexane protons at δ = 3.15 (2H, m, -H^a), 1.92 (2H, m, -H^b + H^c), 1.82 (2H, m, -H^b + H^c), 1.63 (2H, m, -H^b + H^c) and 1.41 (2H, m, -H^b + H^c). In addition, other protons resonate at δ = 7.94 (2H, s, -C***H***=N), 13.66 (2H, s, broad, -O***H***) and 2.94 (12H, s, -N(C$\boldsymbol{H_3}$)$_2$). The aromatic protons show signals at δ = 6.89 (2H, d, ^{3}J = 8.5, -H^e), 6.14 (2H, d, ^{4}J = 2.5, -H^f) and 6.07 (2H, s, -H^h). No long range coupling is noticed here comparing to **(VII)**.

The ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum for **(X)** (Table 3.23; Figure 3.24a) shows signals at δ = 165.4 ppm for (C-1), 108.7 ppm for (C-2), 132.9 ppm for (C-3), 103.5 ppm for (C-4), 153.9 ppm for (C-5), 98.9 ppm for (C-6), 40.1 ppm for (C-7), 163.1 ppm for (C-8), 70.9 ppm for (C-9), 33.2 ppm for (C-10) and 24.4 ppm for (C-11).

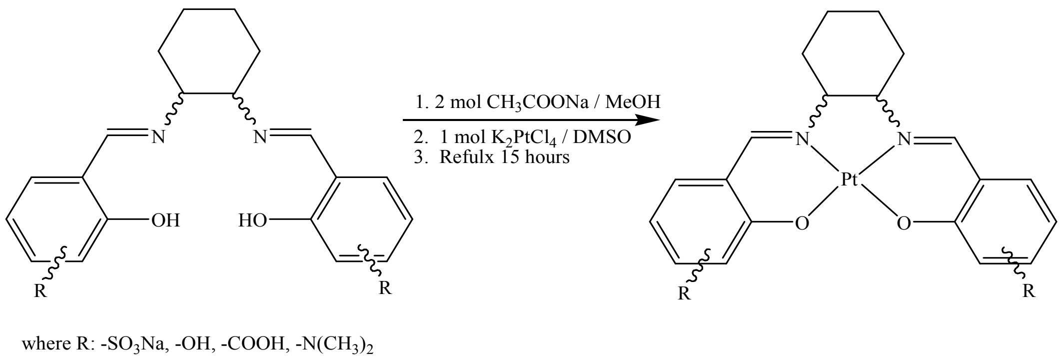
The above NMR spectral data were confirmed using the DEPT-135 experiment (Figure 3.24b) which shows the disappearance of the quaternary carbons at δ: 165.4

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ppm (C-1), 108.7 ppm (C-2) and 153.9 ppm (C-5), and inversion of -CH_2- carbons resonate at δ = 33.2 ppm (C-10) and 24.4 ppm (C-11).

4.3 Preparation of Platinum Complexes:

All complexes were prepared under anhydrous conditions by addition the suitable Schiff base (**n** moles) to methanolic solution of anhydrous sodium acetate (**2n** moles), followed by addition of DMSO solution containing potassium tetrachloropaltinate(II) (**n** moles), as shown below (Che, et al., 2010):

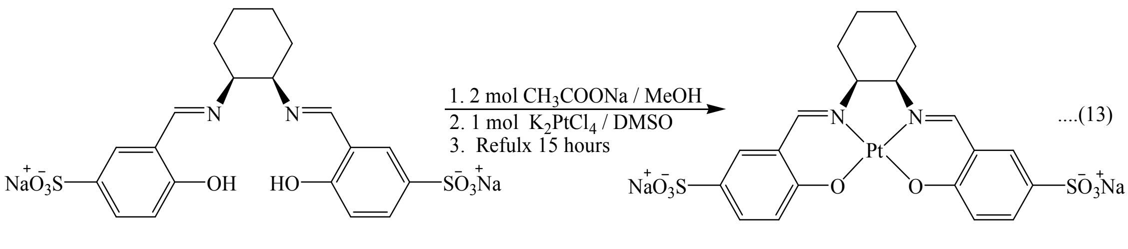


....(12)

4.3.1 Preparation of Platinum Complexes with Schiff Bases Containing *cis*-DACH Ligands:

4.3.1.a Preparation of (XI):

The title compound was prepared, as shown below:



....(13)

Compound **(XI)** was collected as yellow powder; the compound is water-soluble and does not melt or decompose below 360.0 °C. Compound **(XI)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(XI)** (Figure 3.51) shows a strong band at 1603 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. Upon comparison of this value to $\upsilon_{C=N}$ of the free ligand **(IV)** 1632 cm^{-1}, it is noticed the shift of $\upsilon_{C=N}$ in the complex to a lower wave number which can be explained due to the

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formation of Pt-N bond. The broad band was assigned to the $\upsilon_{O\text{-}H}$ in **(IV)** disappeared in the complex which supports the bonding of Pt with phenolic O atom of the Schiff base. Strong vibration bands at 1036, 1116, and 1186 cm^{-1} were assigned to the sulfonyl group.

The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(XI)** (Table 3.24; Figure 3.25) shows all characteristic signals of the ligand, (with the exception of of the phenolic proton), at δ = 3.96 (2H, m, -H^a), 2.33 (2H, m, -H^b + H^c), 1.80 (2H, m, -H^b + H^c), 1.39 (4H, m, -H^b + H^c), 8.52 (2H, s, -C***H***=N), 7.84 (2H, d, ^{4}J = 1. 8, -H^e), 7.59 (2H, d, ^{3}J = 8.8, ^{4}J = 1.8, -H^f) and 6.80 (2H, d, ^{3}J =8.8, -H^h).

The signal at -H^a (2H, m) was downfield shifted (3.96 ppm), whereas, the signal of -C***H***=N (2H, s,) was upfield shifted (8.52 ppm) as compared with the corresponding signals of the ligand 3.67 and 8.60, respectively. This is due to Pt-bonding to the azomethine nitrogen.

The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(XI)** (Table 3.25; Figure 3.26a) shows all characteristic signals for the ligand at δ = 136.7 ppm for (C-1), 131.8 ppm for (C-2), 121.2 ppm for (C-3), 162.8 ppm for (C-4), 120.4 ppm for (C-5), 131.8 ppm for (C-6), 155.3 ppm for (C-7) 70.8 ppm for (C-8), 27.4 ppm for (C-9) and 21.4 ppm for (C-10).

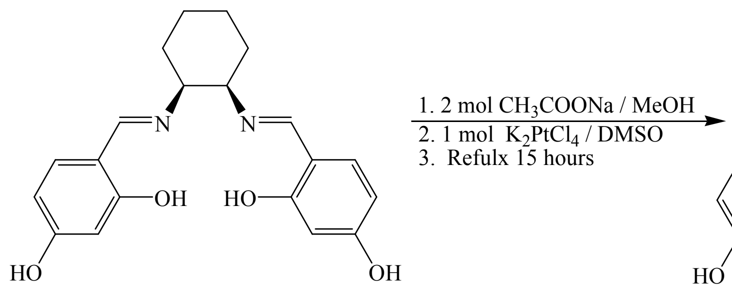
The signal at 155.3 ppm for (C-7) assigned for the azomethine carbon shows upfield shift compared with 165.8 in the ligand, due to Pt-bonding with azomethine nitrogen.

The DEPT-135 experiment (Figure 3.26b) shows the disappearance of the quaternary carbons resonating at δ: 136.7 ppm (C-1), 121.2 ppm (C-3) and 162.8 ppm (C-4), and inversion of -CH_2- carbons resonating at δ: 27.4 ppm (C-9) and 21.4 (C-10).

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4.3.1.b Preparation of (XII):

The title compound was prepared, as shown below:



.......(14)

Compound **(XII)** was collected as orange powder; The compound is water-insoluble and melts at 300.0 - 302.0 °C which is higher than the corresponding in the ligand (260.0 - 262.0 °C). Compound **(XII)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(XII)** (Figure 3.52) shows a strong band at 1605 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. Upon comparison of this value to $\upsilon_{C=N}$ of the free ligand **(V)** 1634 cm^{-1}, it is noticed the shift of $\upsilon_{C=N}$ in the complex to a lower wave number which can be explained due to the formation of Pt-N bond. The broad band was assigned to the υ_{O-H} in **(V)** disappeared in the complex which supports the bonding of Pt with phenolic O atom of the Schiff base. The other band assigned to the υ_{O-H} in ligand **(V)** appeared in the complex at 3451 cm^{-1}.

The ^{1}H-NMR (300 MHz, DMSO-d$_6$) spectrum for **(XII)** (Table 3.26; Figure 3.27) shows all characteristic signals of the ligand, (with the exception of of the phenolic proton), at δ = 3.80 (2H, m, -H^a), 2.16 (2H, m, -H^b + H^c), 1.76 (2H, m, -H^b + H^c), 1.36 (4H, m, -H^b + H^c), 8.14 (2H, s, -C***H***=N), 7.30 (2H, d, ^3J = 8.0, -H^e), 6.10 (2H, d, ^3J = 8.0, -H^f), 6.22 (2H, s, -H^h) and 9.82 (2H, s, - H^g).

The signal at -H^a (2H, m) was downfield shifted (3.80 ppm), whereas, the signal of -C***H***=N (2H, s,) was upfield shifted (8.14 ppm) as compared with the corresponding signals of the ligand 3.54 and 8.32, respectively. This is due to Pt-bonding to the azomethine nitrogen.

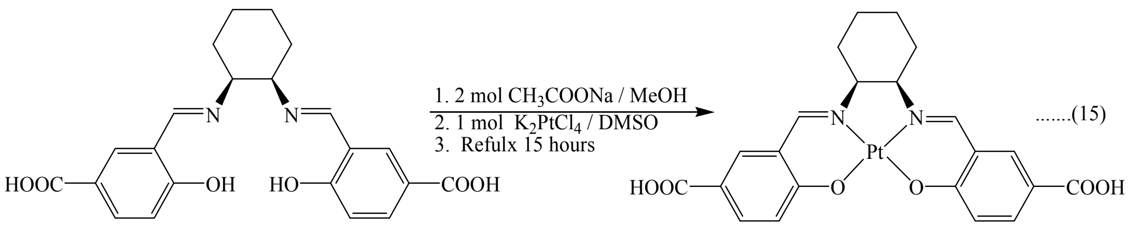
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The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(XII)** (Table 3.27; Figure 3.28) shows all characteristic signals for the ligand at δ = 163.2 ppm for (C-1), 105.0 ppm for (C-2), 164.9 ppm for (C-3), 116.6 ppm for (C-4), 136.0 ppm for (C-5), 107.0 ppm for (C-6), 153.5 ppm for (C-7), 70.3 ppm for (C-8), 27.3 ppm for (C-9) and 21.5 ppm for (C-10).

The signal at 153.5 ppm for (C-7) assigned to the azomethine carbon shows upfield shift compared with 164.4 in the ligand, due to Pt-bonding with azomethine nitrogen.

4.3.1.c Preparation of (XIII):

The title compound was prepared, as shown below:



.......(15)

Compound **(XIII)** was collected as yellow powder; The compound is water-insoluble and melts at 310.0 - 312.0 °C comparing the corresponding ligand (285-287°C). Compound **(XIII)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(XIII)** shows a strong band at 1603 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. Upon comparison of this value to $\upsilon_{C=N}$ of the free ligand **(VI)** 1633 cm^{-1}, the $\upsilon_{C=N}$ of the complex is shifted to a lower wave number which is an indication of Pt-N bond formation. The broad band was assigned to the υ_{O-H} in **(VI)** disappeared in the complex which supports the bonding of Pt with phenolic O atom of the Schiff base. The other band was assigned to the υ_{O-H} in **(VI)** in the complex is at 2584 cm^{-1} which represents the carboxyl -OH.

The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(XIII)** (Table 3.28; Figure 3.29) shows all characteristic signals of the ligand, (with the exception of of the

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phenolic proton), at δ = 4.00 (2H, m, -H^a), 1.82 (3H, m, -H^b + H^c), 1.39 (5H, m, -H^b + H^c), 8.30 (2H, s, -C***H***=N), 8.30 (2H, s, broad, -H^e), 7.91 (2H, s, broad, -H^g), 6.90 (2H, s, broad, - H^h) and 12.41 (2H, s, broad, -H^f).

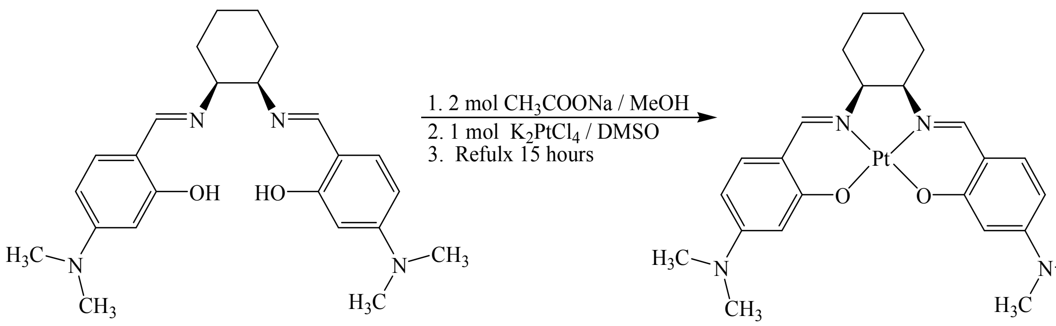
The signal at -H^a (2H, m) was downfield shifted (3.80 ppm), whereas, the signal of -C***H***=N (2H, s,) was upfield shifted (8.30 ppm) as compared with the corresponding signals of the ligand 3.75 and 8.68, respectively. This is due to Pt-bonding to the azomethine nitrogen. No couplings were noticed between adjacent protons. The OH proton of carboxylic acid resonates at δ: 12.41.

The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(XIII)** (Table 3.29; Figure 3.30) shows all characteristic signals for the ligand at δ = 138.2 ppm for (C-1), 134.3 ppm for (C-2), 122.7 ppm for (C-3), 165.9 ppm for (C-4), 118.6 ppm for (C-5), 138.2 ppm for (C-6), 167.2 ppm for (C-7), 156.0 ppm for (C-8), 71.1 ppm for (C-9), 27.3 ppm for (C-10) and 21.4 ppm for (C-11).

The signal at 156.0 ppm for (C-8) assigned to the azomethine carbon shows upfield shift compared with 166.8 in the ligand, due to Pt-bonding with azomethine nitrogen.

4.3.1.d Preparation of (XIV):

The title compound was prepared, as shown below:



......(16)

Compound **(XIV)** was collected as yellow powder; The compound is water-insoluble and melts at 280.0 - 282.0 °C which is higher than the corresponding melting point of the ligand (190.0 - 192.0°C). Compound **(XIV)** was characterized by its IR, ^{1}H-

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NMR and ^{13}C-NMR spectra. The IR spectrum of **(XIV)** (Figure 3.53) shows a strong band at 1596 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. Upon comparison of this value to $\upsilon_{C=N}$ of the free ligand **(VII)** 1615 cm^{-1}, it is noticed the shift of $\upsilon_{C=N}$ in the complex to a lower wave number which can be explained due to the formation of Pt-N bond. The broad band was assigned to the υ_{O-H} in **(VII)** disappeared in the complex which supports the bonding of Pt with phenolic O atom of the Schiff base.

The ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum for **(XIV)** (Table 3.30; Figure 3.31) shows all characteristic signals of the ligand, (with the exception of of the phenolic proton), at δ = 3.72 (2H, m, -H^a), 2.24 (4H, m, -H^b + H^c), 1.52 (2H, m, -H^b + H^c), 7.69 (2H, s, -C***H***=N), 2.59 (12H, s, -N(C***H₃***)₂), 7.09 (2H, d, ^{3}J = 9.0, -H^e), 6.11 (2H, d, ^{3}J = 9.0, -H^f) and 6.46 (2H, s, -H^h).

The signal at -H^a (2H, m) was downfield shifted (3.72 ppm), whereas, the signal of -C***H***=N (2H, s,) was upfield shifted (7.69 ppm) as compared with the corresponding signals of the ligand 3.49 and 8.02, respectively. This is due to Pt-bonding to the azomethine nitrogen.

The ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum for **(XIV)** (Table 3.31; Figure 3.32a) shows all characteristic signals for the ligand resonate at δ = 164.9 ppm for (C-1), 109.1 ppm for (C-2), 134.4 ppm for (C-3), 103.6 ppm for (C-4), 154.7 ppm for (C-5), 102.4 ppm for (C-6), 40.3 ppm for (C-7), 150.9 ppm for (C-8), 70.4 ppm for (C-9), 27.4 ppm for (C-10) and 21.5 ppm (C-11).

The signal at 150.9 ppm for (C-8) assigned to the azomethine carbon shows upfield shift compared with 162.4 in the ligand, due to Pt-bonding with azomethine nitrogen.

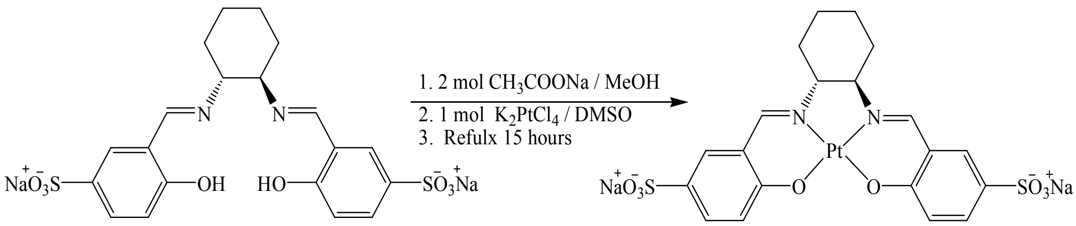
The DEPT-135 experiment (Figure 3.32b) shows the disappearance of the quaternary carbons at δ = 164.9 ppm (C-1), 109.1 ppm (C-2) and 154.7 ppm (C-5), and inversion of -CH_2- carbons resonating at δ: 27.4 ppm (C-10) and 21.5 (C-11).

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4.3.2 Preparation of Platinum Complexes with Schiff Bases Containing *trans*-DACH Ligands:

4.3.2.a Preparation of (XV):

The title compound was prepared, as shown below:



...(17)

Compound **(XV)**was collected as yellow powder; The compound is water-soluble and does not melt below 360.0 °C. Compound **(XV)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(XV)** (Figure 3.54) shows a strong band at 1603 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. Upon comparison of this value to $\upsilon_{C=N}$ of the free ligand **(VIII)** 1633 cm^{-1}, it is noticed the shift of $\upsilon_{C=N}$ in the complex to a lower wave number which can be explained due to the formation of Pt-N bond. The broad band was assigned to the $\upsilon_{O\text{-}H}$ in VIII) disappeared in the complex which supports the bonding of Pt with phenolic O atom of the Schiff base. Strong vibration bands at 1035, 1114, and 1182 cm^{-1} were assigned to the sulfonyl group.

The ^{1}H-NMR (300 MHz, DMSO-d$_6$) spectrum for **(XV)** (Table 3.32; Figure 3.33) shows all characteristic signals of the ligand, (with the exception of of the phenolic proton), at δ = 3.51 (2H, m, -H^a), 1.73 (3H, m, -H^b + H^c) and 1.30 (5H, m,-H^{b+c}), 8.45 (2H, s, -C***H***=N), 7.91 (2H, d, ^4J = 1.7, -H^e), 7.58 (2H, dd, ^3J = 8.8, ^4J = 1.7, -H^f) and 6.79 (2H, d, ^3J =8.8, -H^h).

The signal at -C***H***=N (2H, s,) was upfield shifted (8.45 ppm) as compared with the corresponding signal of the ligand, (8.53 ppm). This is due to Pt-bonding to the azomethine nitrogen.

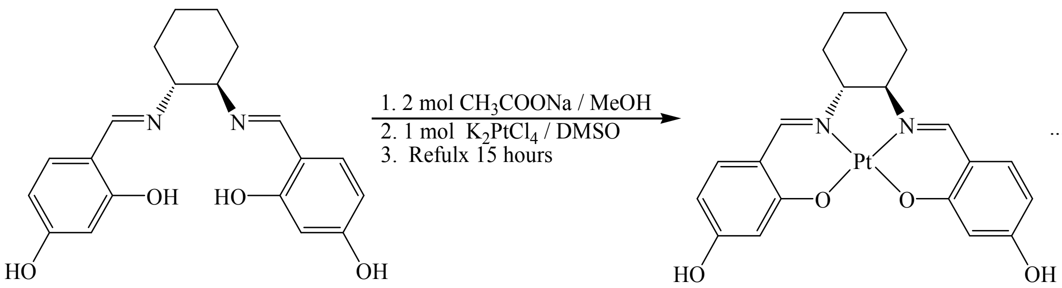
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The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(XV)** (Table 3.33; Figure 3.34) shows all characteristic signals for the ligand at δ = 136.6 ppm for (C-1), 132.2 ppm for (C-2), 121.0 ppm for (C-3), 163.1 ppm for (C-4), 120.4 ppm for (C-5), 131.9 ppm for (C-6), 153.1 ppm for (C-7), 74.2 ppm for (C-8), 27.9 ppm for (C-9) and 24.7 ppm for (C-10).

The signal at 153.1 ppm for (C-7) assigned for the azomethine carbon shows upfield shift compared with 165.5 in the ligand, due to Pt-bonding with azomethine nitrogen.

4.3.2.b Preparation of (XVI):

The title compound was prepared, as shown below:



...... (18)

Compound **(XVI)** was collected as orange powder; The compound is water-insoluble and melts at 305.0 - 307.0 °C which is higher than the corresponding melting point of the ligand (250.0 - 252.0 °C). Compound **(XVI)** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(XVI)** (Figure 3.55) shows a strong band at 1605 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. Upon comparison of this value to $\upsilon_{C=N}$ of the free ligand **(IX)** 1633 cm^{-1}, it is noticed the shift of $\upsilon_{C=N}$ in the complex to a lower wave number which can be explained due to the formation of Pt-N bond. The broad band was assigned to the υ_{O-H} in **(IX)** disappeared in the complex which supports the bonding of Pt with phenolic O atom of the Schiff base. The other band assigned to the υ_{O-H} in **(IX)** in the complex is at 3446 cm^{-1}.

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The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum for **(XVI)** (Table 3.34; Figure 3.35) shows all characteristic signals of the ligand, (with the exception of of the phenolic proton), at δ = 2.62 (2H, m, - H^a), 1.73 (3H, m,- H^b + H^c), 1.36 (5H, m,- H^b + H^c), 8.07 (2H, s, -C***H***=N), 7.33 (2H, d, ^3J = 8.0, -H^e), 6.09 (2H, d, ^3J = 8.0, -H^f), 6.20 (2H, s, -H^h) and 9.84 (2H, s, -H^g).

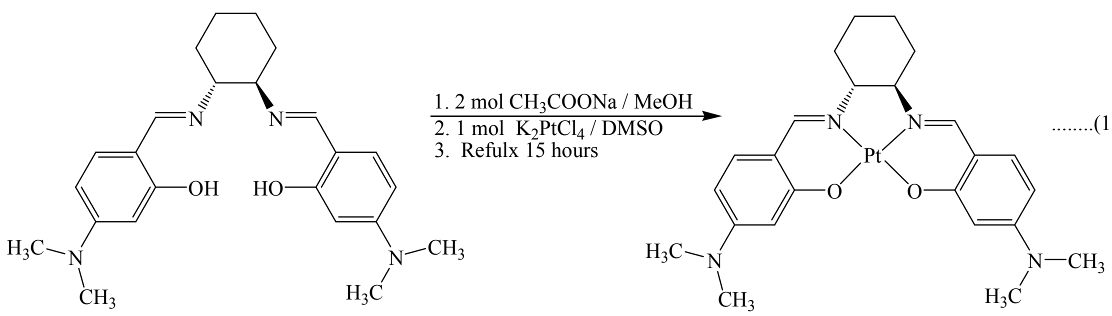
The signal at -C***H***=N (2H, s,) was upfield shifted (8.07 ppm) as compared with the corresponding signals of the ligand (8.23 ppm). This is due to Pt-bonding to the azomethine nitrogen.

The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum for **(XVI)** (Table 3.35; Figure 3.36) shows all characteristic signals for the ligand at δ = 163.2 ppm for (C-1), 105.0 ppm for (C-2), 165.2 ppm for (C-3), 116.4 ppm for (C-4), 136.4 ppm for (C-5), 106.9 ppm for (C-6), 151.3 ppm for (C-7), 73.7 ppm for (C-8), 28.0 ppm for (C-9) and 24.3 ppm for (C-10).

The signal at 151.3 ppm for (C-7) assigned to the azomethine carbon shows upfield shift compared with 164.3 in the ligand, due to Pt-bonding with azomethine nitrogen.

4.3.2.c Preparation of (XVII):

The title compound was prepared, as shown below:



........(19)

Compound **(XVII)** was collected as yellow powder; The compound is water-insoluble and does melt below 360.0 °C which is higher than the corresponding melting point of the ligand (167.0 - 169.0 °C). Compound **(XVII)** was characterized by its IR,

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^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of **(XVII)** (Figure 3.56) shows a strong band at 1594 cm^{-1} was assigned to $\upsilon_{C=N}$ of the azomethine group. Upon comparison of this value to $\upsilon_{C=N}$ of the free ligand **(X)** 1617 cm^{-1}, it is noticed the shift of $\upsilon_{C=N}$ in the complex to a lower wave number which can be explained due to the formation of Pt-N bond. The broad band was assigned to the $\upsilon_{O\text{-}H}$ in **(X)** disappeared in the complex which supports the bonding of Pt with phenolic O atom of the Schiff base.

The ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum for Compound (Table 3.36; Figure 3.37) shows all characteristic signals of the ligand, (with the exception of of the phenolic proton), at δ = 3.18 (2H, m, -H^a), 1.90 (2H, m, -H^b + H^c), 1.84 (2H, m, -H^b + H^c), 1.53 (2H, m, -H^b + H^c) and 1.41 (2H, m, -H^b + H^c), 7.95 (2H, s, -C***H***=N), 2.96 (12H, s, -N(C$\boldsymbol{H_3}$)$_2$), 6.89 (2H, d, ^3J = 8.7, -H^e), 6.08 (2H, d, ^3J = 8.7, ^4J = 2.3, -H^f), 6.04 (2H, d, ^4J = 2.3, -H^h).

The signal at -H^a (2H, m) was downfield shifted (3.18 ppm), whereas, the signal of -C***H***=N (2H, s,) was upfield shifted (7.95 ppm) as compared with the corresponding signals of the ligand 3.15 and 7.99, respectively. This is due to Pt-bonding to the azomethine nitrogen.

The ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum for Compound (Table 3.37; Figure 3.38) shows all characteristic signals for the ligand at δ = 99.9 ppm for (C-2), 128.1 ppm for (C-3), 98.6 ppm for (C-4), 130.5 ppm for (C-5), 94.2 ppm for (C-6), 35.4 ppm for (C-7), 158.4 ppm for (C-8), 66.2 ppm for (C-9) and 28.5 ppm for (C-10).

The signal at 158.4 ppm for (C-8) assigned to the azomethine carbon shows upfield shift compared with 163.1 in the ligand, due to Pt-bonding with azomethine nitrogen.

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CONCLUSIONS AND RECOMMENDATIONS

Some salicylaldehydes **(I,II and III)** have been prepared with the substituents -SO_3Na, -COOH and -$N(CH_3)_2$, repectively. The substituted aldehydes were then used in the synthesis of new tetradentate Schiff base ligands **(IV-X)**. The substituents on salicylaldeyhde are chosen in a way to increase the hydrophilic character of the Schiff bases and consequently their platinum complexes.

Some of the platinum complexes show good water-solubility **(XI** and **XV)**. The other complexes can be converted to water-soluble ones via converting the Schiff base ligands to either sodium salts or ammonium salts

Several attempts to synthesize the reduced form of the Schiff base ligands (amine ligands) using $NaBH_4$ were unsuccessful. Therefore, it is suggested to adapt the catalytic reduction process rather than the simple reduction via $NaBH_4$ to convert the Schiff base ligands to amine ligands. Consequently, further work still needed to prepare and isolate the reduced form of the Schiff base and their platinum complexes.

On the other hand, due to the high sensitivity of Schiff base ligands to hydrolysis in basic aqueous solutions, platinum precursors other than K_2PtCl_4 are recommended for future work. One of the suggested precursors is $Pt(C_6H_5CN)_2Cl_2$ which has a good solubility in organic solvents. In addition to that, other groups can be also added on salicylaldehydes such as (tetraalkylammonium and tetraalkylphosphonium) which is expected to show good water-solubility.

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معقدات البلاتين الذائبة في الماء كأدوية لمعالجة السرطان

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المشرف
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الملخص

تم تحضير مجموعة من متصلات شيف رباعية الارتباط التناسقي ، وهي : ملح صوديوم (٣،٣`-(مجاور-١،٢-ثنائي(نيتريلوميثليدين)الهكسيل الحلقي)ثنائي-٤-هيدروكسي حمض البنزين الكبريتوزي)**IV) )** ، (٤،٤`-(مجاور-١،٢- ثنائي(نيتريلوميثليدين) الهكسيل الحلقي)ثنائي-1،٣-ثنائي هيدروكسي بنزين) ، (٣،٣`-(مجاور-١،٢- ثنائي (نيتريلوميثليدين)الهكسيل الحلقي)ثنائي-٤-هيدروكسي حمض البنزويك) **(VI)** ، (٢،٢`-(مجاور-١،٢-ثنائي(نيتريلوميثليدين)الهكسيل الحلقي)ثنائي-((٥-(N،N)-ثنائي ميثيل أمينو) فينول) **(VII)** ، ملح صوديوم (٣،٣`-(مضاد-١،٢-ثنائي(نيتريلوميثليدين)الهكسيل الحلقي)ثنائي-٤-هيدروكسي حمض البنزين الكبريتوزي) **(VIII)** ، (٤،٤`-(مضاد-١،٢-ثنائي(نيتريلوميثليدين)الهكسيل الحلقي)ثنائي-1،٣- ثنائي هيدروكسي بنزين) **(IX)** ، (٢،٢`-(مضاد-١،٢- ثنائي(نيتريلوميثليدين)الهكسيل الحلقي)ثنائي-((٥-(N،N)-ثنائي ميثيل أمينو) فينول) **(X)** ، وقد تمت عملية تحضير المعقدات السابقة من خلال تفاعل اتحاد الساليسالدهايد المتفرع المناسب مع مجاور- أو مضاد-١،٢-ثنائي أمينو الهكسان الحلقي بنسبة مولية (٢ : ١) على التوالي ، حيث تم اختيار المتفرعات ($-SO_3Na$,-OH,-COOH,-$N(CH_3)_2$) لزيادة ذائبية قواعد شيف في الماء وبالتالي زيادة ذائبية معقداتها البلاتينية ، وقد تم التعرف على هذه المتصلات وشخصت من خلال جهاز الاشعة تحت الحمراء (IR) وجهاز الرنين المغناطيسي النووي لكل من عنصري الهيدروجين والكربون (^{1}H-NMR and ^{13}C-NMR) ، وعند تفاعل المتصلات السابقة مع ملح رباعي كلورو بلاتين (II) البوتاسيوم K_2PtCl_4 بوجود اسيتات الصوديوم اللامائية تم الحصول على معقدات البلاتين التالية :**XI))** و **(XII)** و**XIII))** و **(XIV)** و **XV))** و **(XVI)** و **(XVII)** على التوالي. وقد تم التعرف على هذه المعقدات وشخصت من خلال جهاز الاشعة تحت الحمراء (IR) وجهاز الرنين المغناطيسي النووي لكل من عنصري الهيدروجين والكربون (^{1}H-NMR and ^{13}C-NMR). الجدير بالذكر أن بعض هذه المعقدات قد أظهر ذوباناً جيداً في الماء مما يقود الى التنبؤ بأن تكون هذه المعقدات ذات فعالية جيدة وسمية قليلة كأدوية لمعالجة السرطان.

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